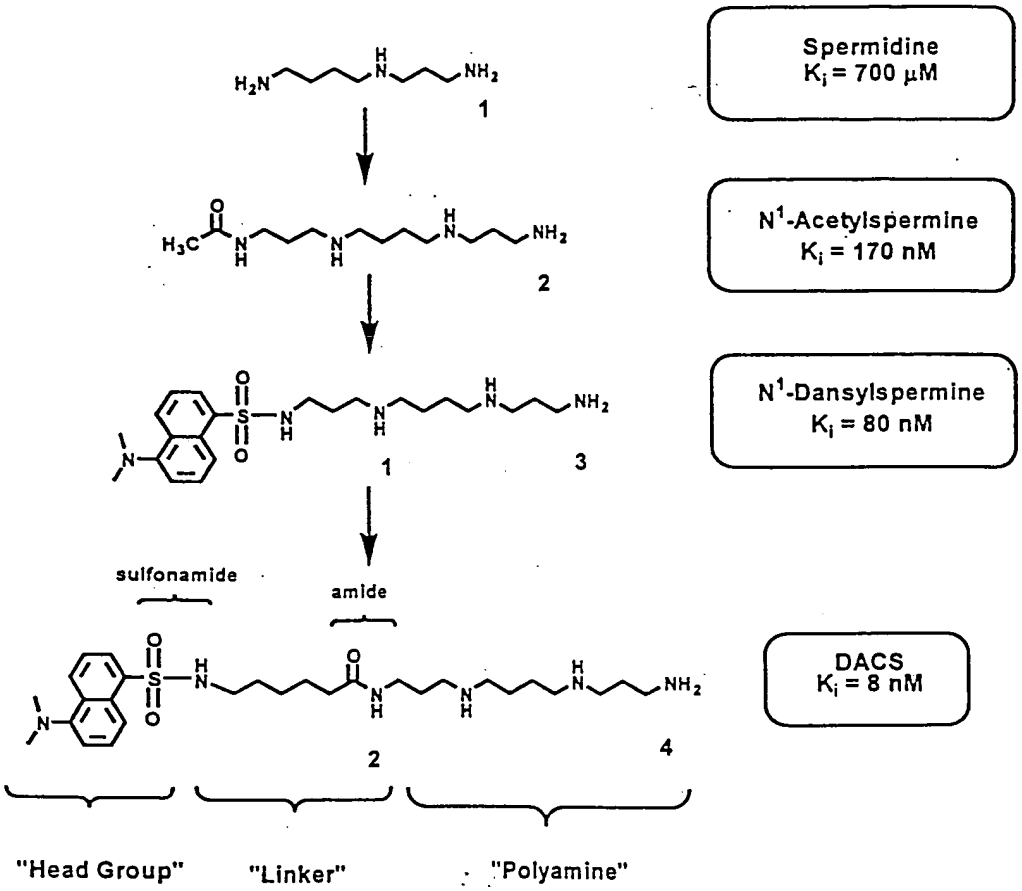
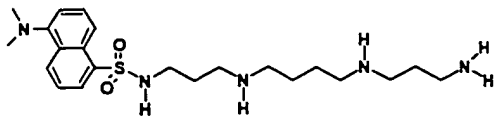
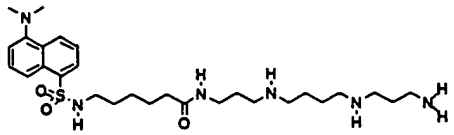
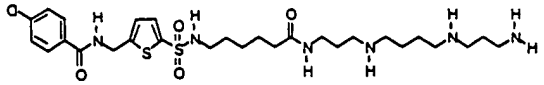
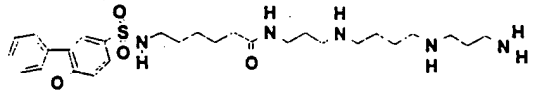
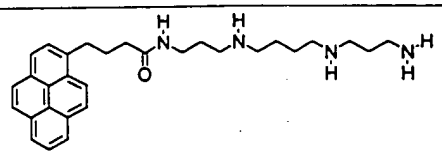
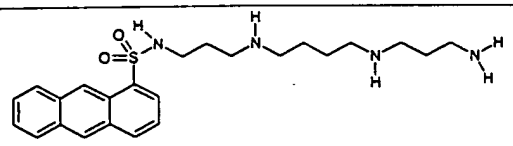
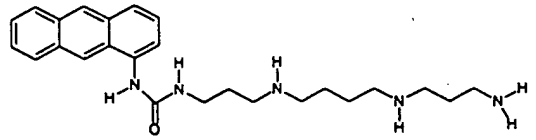
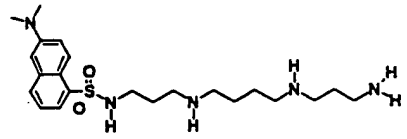
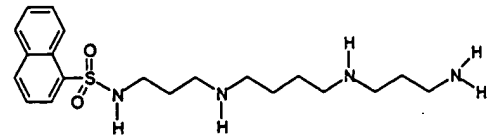
Fig. 1


Spermidine
K_i = 700 μM
N^1-Acetylspermine
K_i = 170 nM
N^1-Dansylspermine
K_i = 80 nM
DACS
K_i = 8 nM
sulfonamide
amide
1
2
3
4
"Head Group"
"Linker"
"Polyamine"

#	Structure	Ki (M)[a]	R[b]	Method[c]
3		0.080	20	I
4		0.010	400	IX, XIII
5		0.010	210	XIII
6		0.005	220	XIII
7		0.10	3.6	III
8		0.110	3.7	II
9		0.440	2.7	IV
10		0.050	>10	XV
11		0.190	2.4	XV

a Inhibition of polyamine uptake: Ki determined from Lineweaver-Burke double reciprocal plots
b Inhibition of Tumor Cell Growth: R is ratio of IC50 (compound alone) to IC50 (compound + DFMO)
c Numbers refer to Examples (describing synthesis)
d Purchased from Aldrich Chemical Company

Fig. 2/1

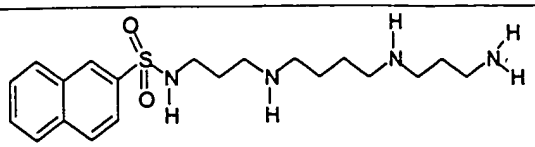
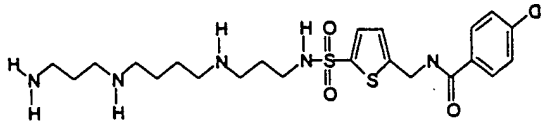
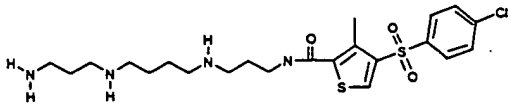
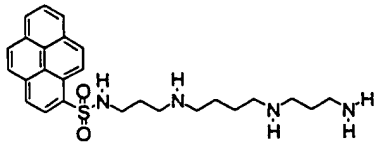
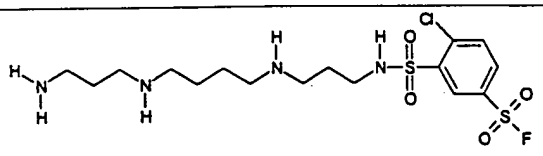
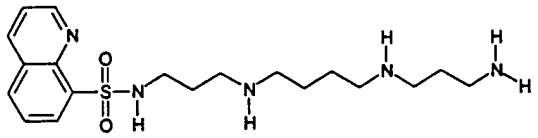
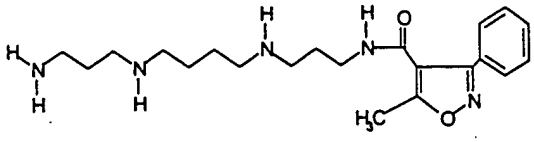
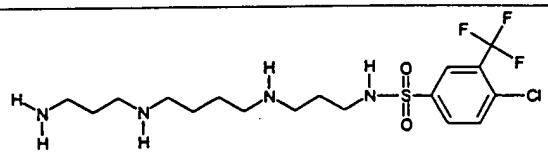
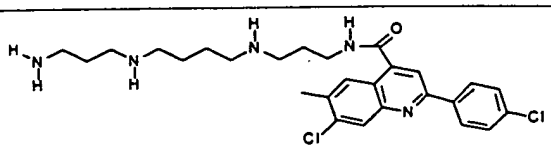
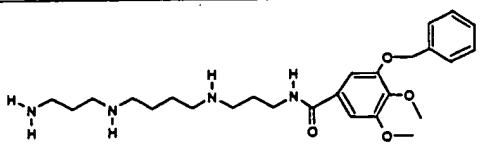
#	Structure	Ki (M)[a]	R[b]	Method[c]
12		0.150	4.3	XV
13		0.058	>47	XV
14		0.037	14	XVII
15		0.091	2.2	II
16		0.08	2.1	XV
17		0.43	>31	XV
18		0.083	40	XVII
19		0.24	>10	XV
20		0.28	1.0	XVII
21		0.084	1.0	XVII

Fig. 2/2

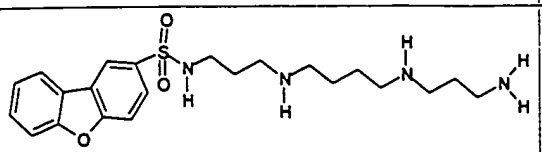
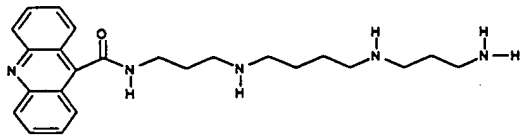
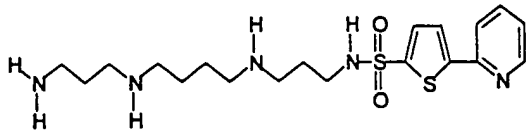
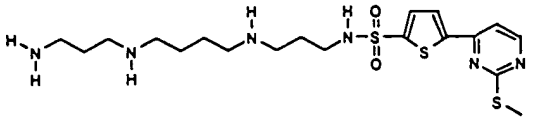
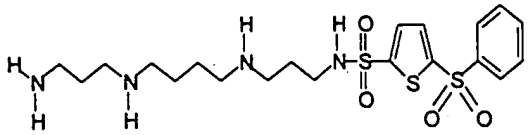
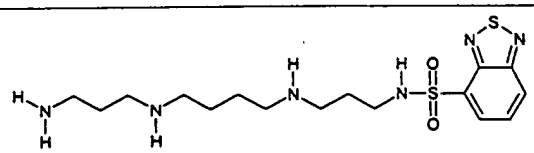
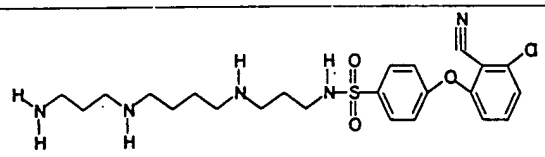
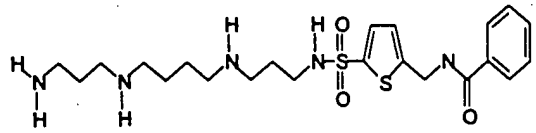
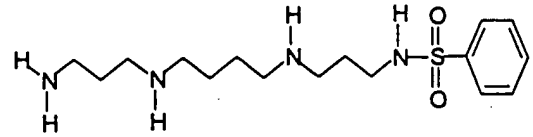
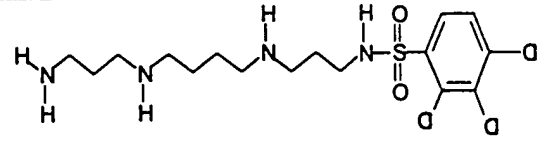
#	Structure	Ki (M)[a]	R[b]	Method[c]
22		0.066	11	XV
23		0.250	6.2	II
24		0.23	10	XV
25		0.067	8.6	XV
26		0.180	15	XV
27		0.650	9.9	XV
28		0.054	9.3	XV
29		0.076	>46	XV
30		0.120	>10	XV
31		0.083	>12	XII

Fig. 2/3

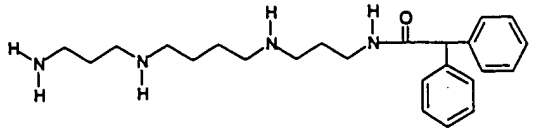
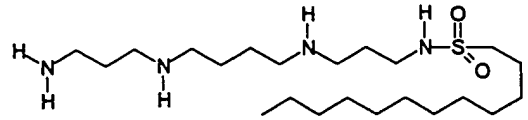
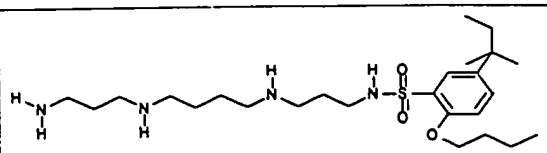
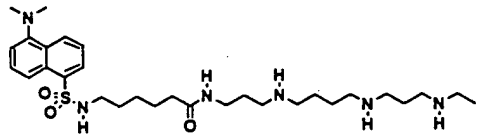
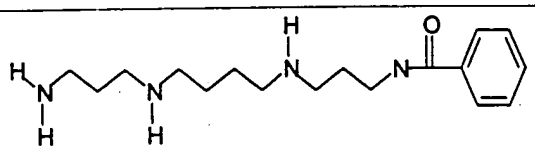
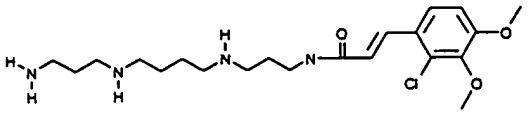
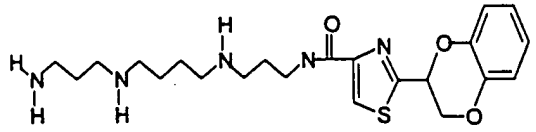
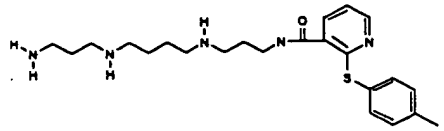
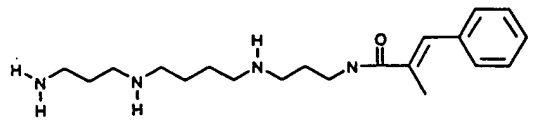
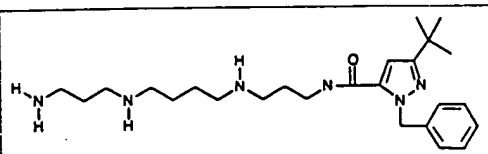
#	Structure	Ki (M)[a]	R[b]	Method[c]
32		0.093	2.1	XVII
33		0.17	1.4	XV
34		0.120	1.0	XV
35		0.041	33	XIII
36		0.61	>2	XVII
37		0.150	2.4	XVII
38		0.140	1.0	XVII
39		0.500	1	XVII
40		0.086	18	XVII
41		0.200	1.0	XVII

Fig. 2/4

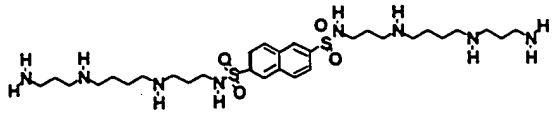
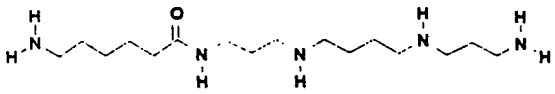
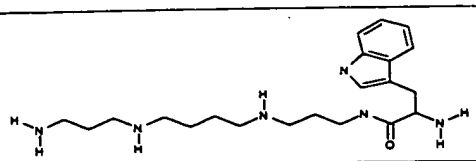
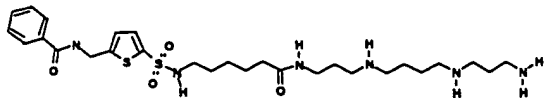
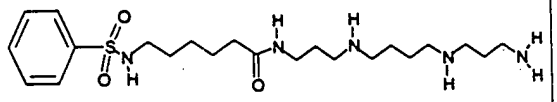
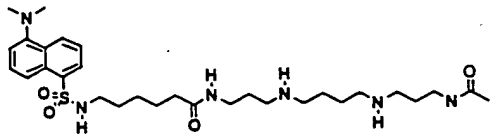
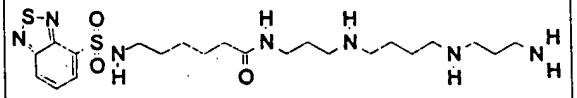
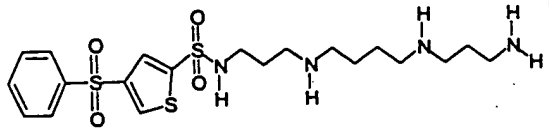
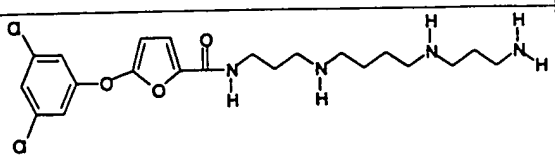
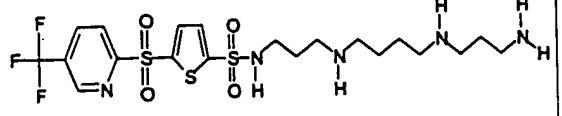
#	Structure	Ki (M)[a]	R[b]	Method[c]
42		0.110	1.1	XIV
43		0.033	76	XVII
44		0.073	39	XIII
45		0.052	3.0	XIII
46		0.082	63	XIII
47		2.1	6.8	XIII
48		0.079	>49	XIII
49		0.067	3.2	XV
50		0.12	1.0	XVII
51		0.083	1.5	XV

Fig. 2/5

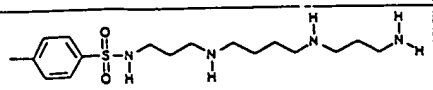
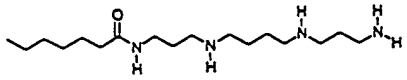
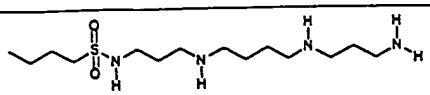
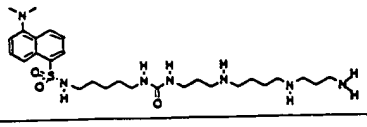
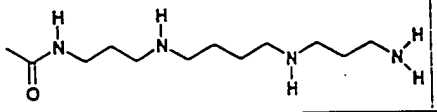
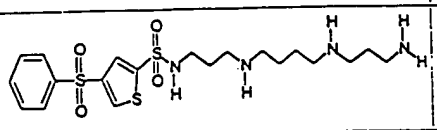
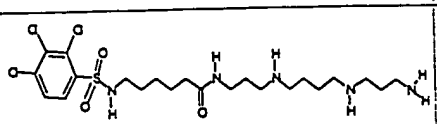
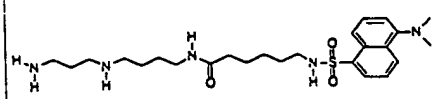
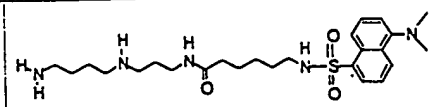
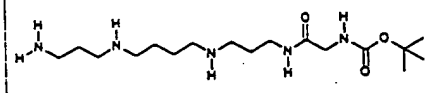
#	Structure	Ki (M)[a]	R[b]	Method[c]
52		0.094	5.3	XV
53		0.18	1.0	XV
54		0.19	2.0	XV
55		0.079	>1.1	IV
56		0.190		d
57		0.017	170	XV
58		0.050	189	XIII
59			>1	XIII
60			>1	XIII
61		0.200	1.0	XIII

Fig. 2/6

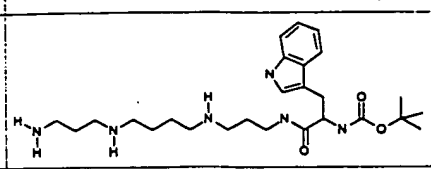
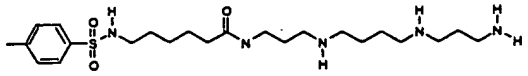
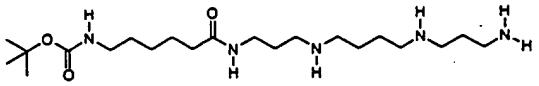
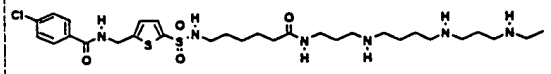
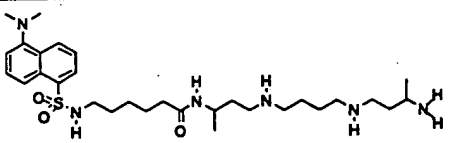
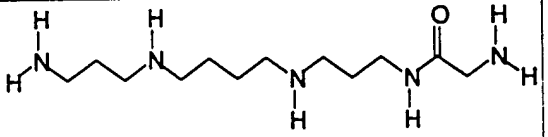
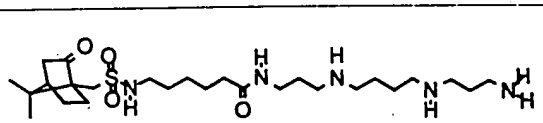
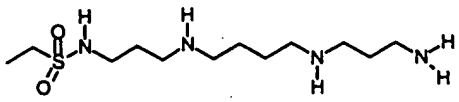
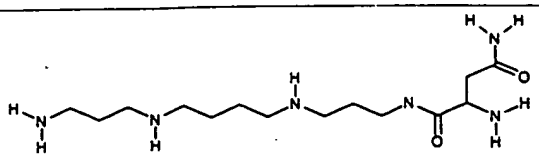
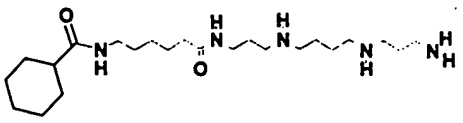
#	Structure	Ki (M)[a]	R[b]	Method[c]
62			>2.0	XIII
63		0.050	>1	XIII
64		0.046		XIII
65		0.012		XIII
66		0.018	27	XIII
67		0.07	1.0	XIII
68		0.110	>4.4	XIII
69		0.22	1	XV
70		0.033	>12.2	XIII
71		0.160	>1.5	XIII

Fig. 2/7

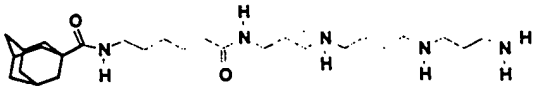
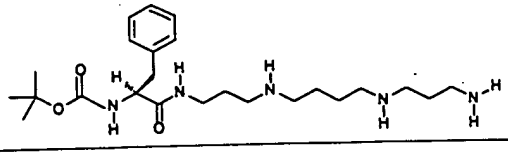
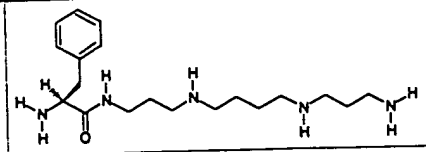
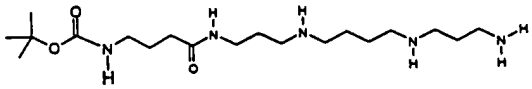
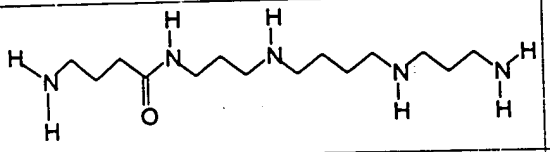
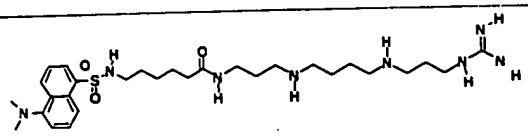
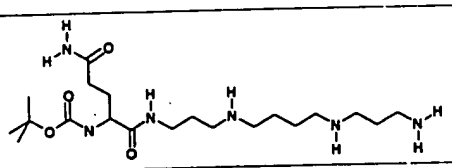
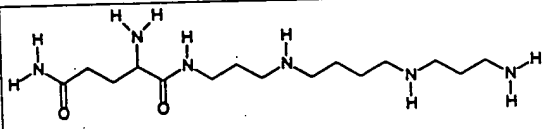
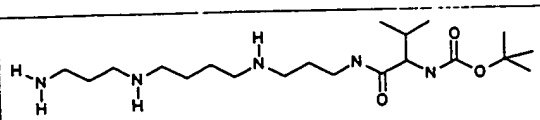
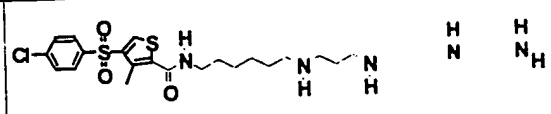
#	Structure	Ki (M)[a]	R[b]	Method[c]
72		0.031	>100	XIII
73		0.094	>1	XIII
74		0.200	1.0	XIII
75		0.130	>1	XIII
76		0.040	1.0	XIII
77		0.093	1	XIII
78		0.156		XIII
79		0.047	1	XIII
80		0.258		XIII
81		0.0096	153	XIII

Fig. 2/8

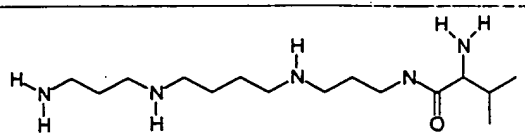
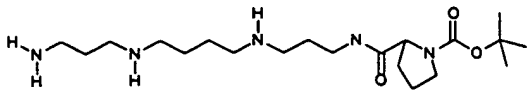
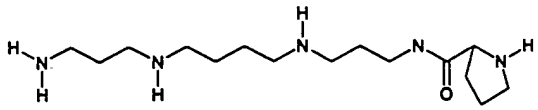
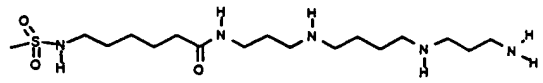
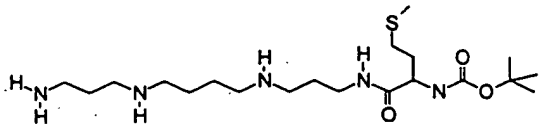
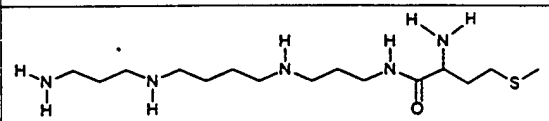
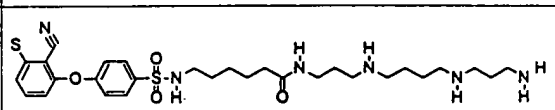
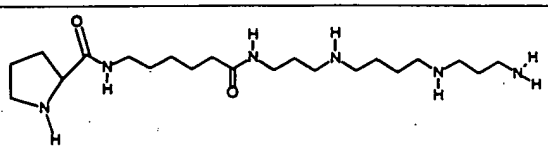
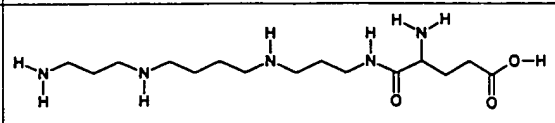
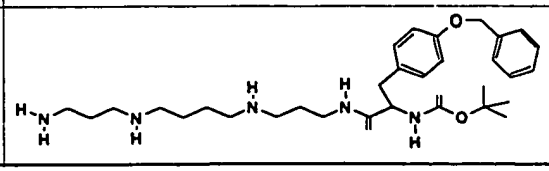
#	Structure	Ki (M)[a]	R[b]	Method[c]
82		0.097	>54	XIII
83		0.183		XIII
84		0.036	>3.2	XIII
85		0.048	>6.5	XIII
86		0.091		XIII
87		0.034	>1	XIII
88		0.014	>40	XIII
89		0.020	>1	XIII
90		0.077		XIII
91		0.037	1	XIII

Fig. 2/9

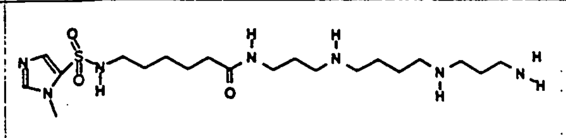
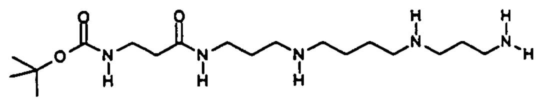
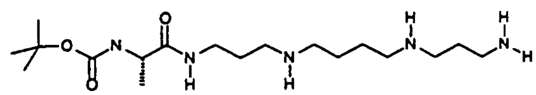
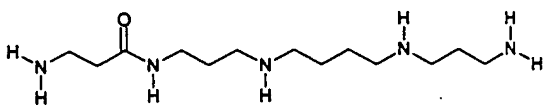
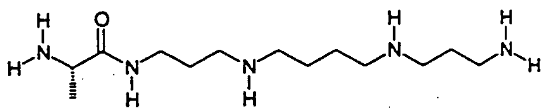
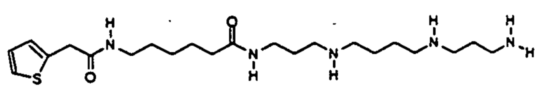
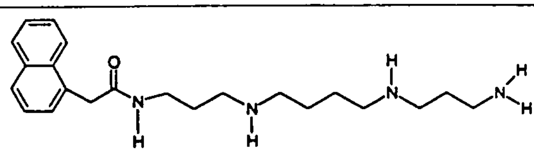
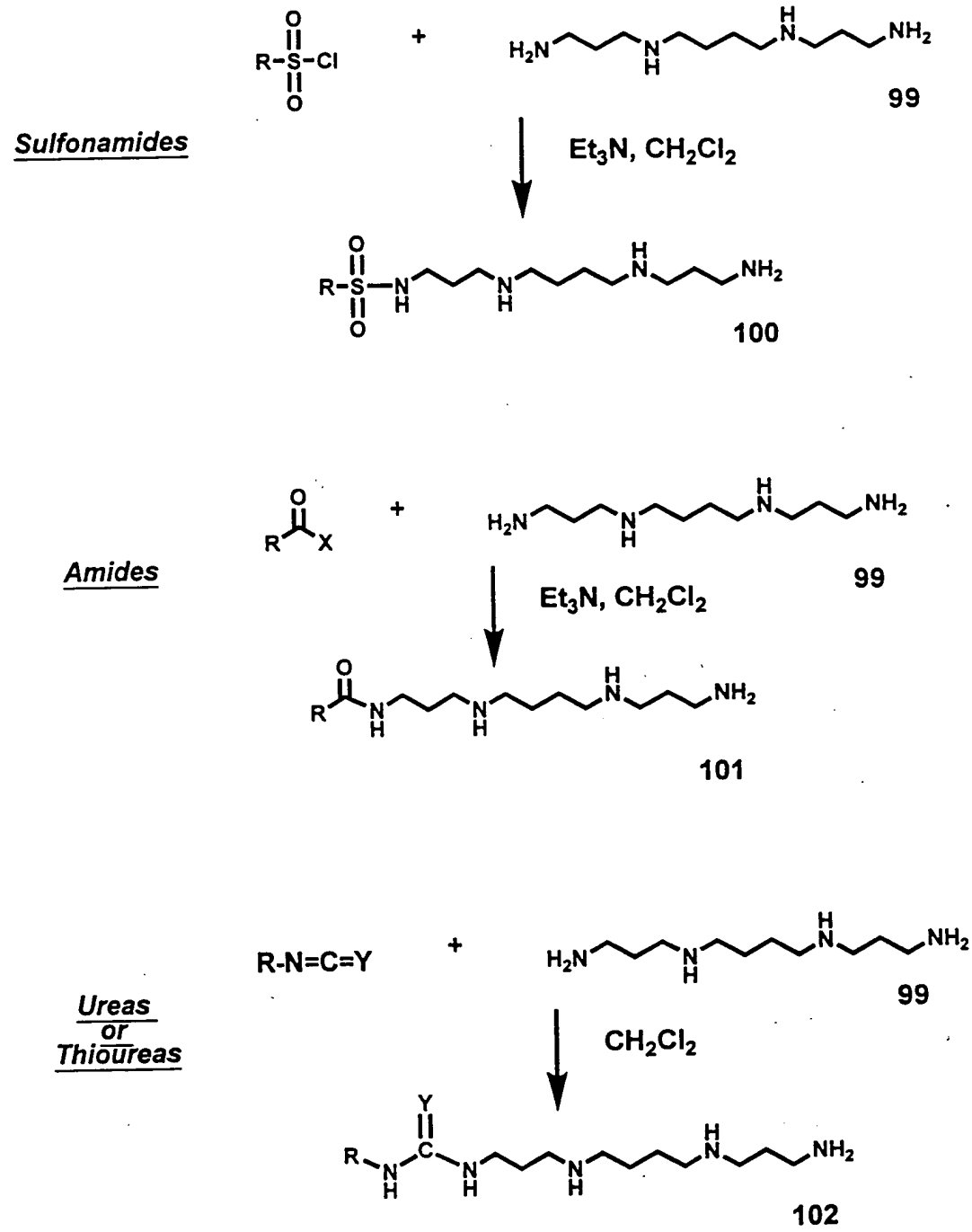
#	Structure	Ki (M)[a]	R[b]	Method[c]
92		0.300	1	XIII
93		0.061	1	XIII
94		0.042	1	XIII
95		0.050	1	XIII
96		0.034	1	XIII
97		0.027	1	XIII
98		0.180	12	d

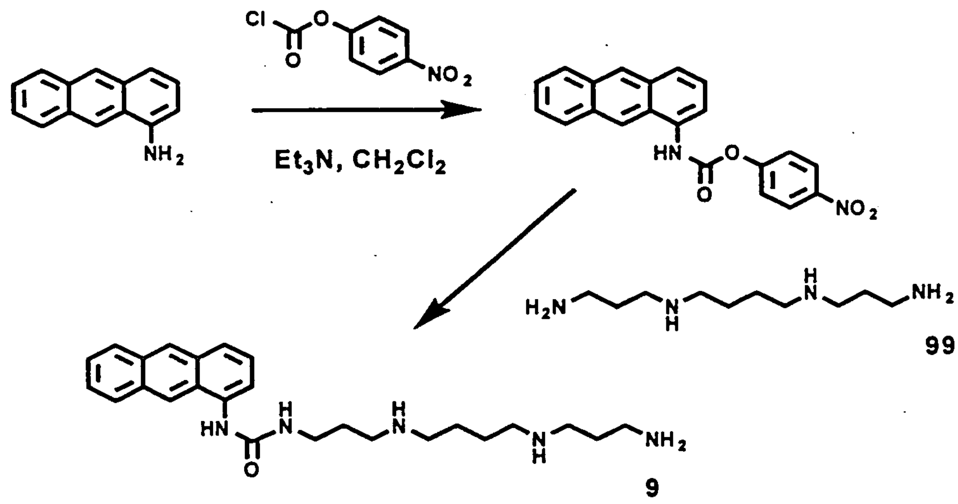
Fig. 2/10

Fig. 3



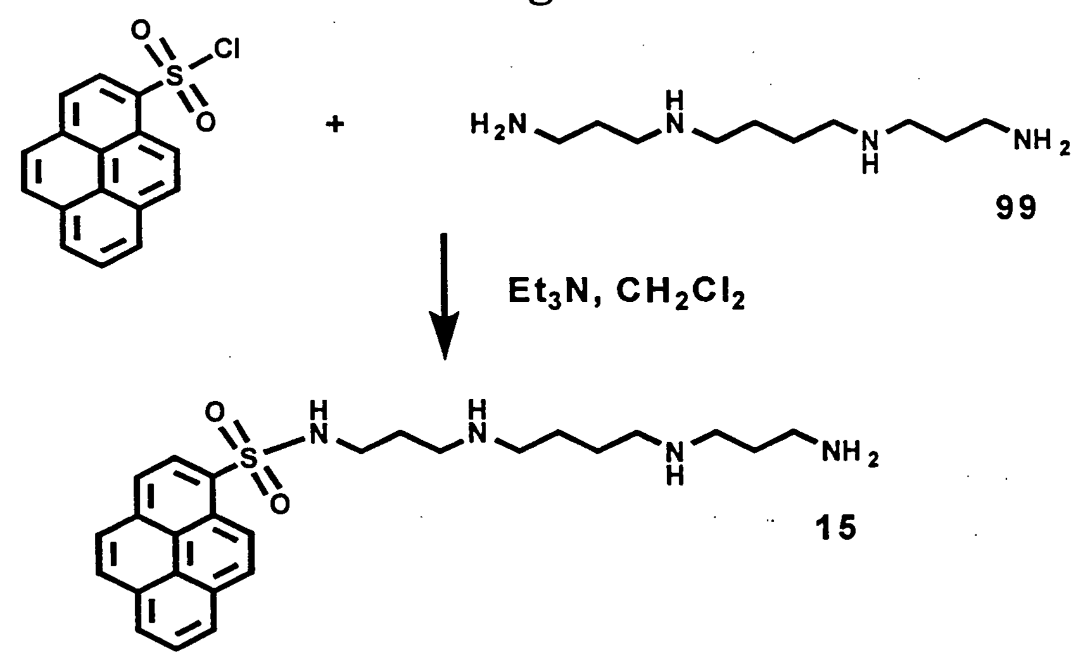
Where X = halide or N-hydroxysuccinimide ester
R = head group
polyamine = spermine (or other)
Y = O or S or NHR
(corresponding to ureas, thioureas and guanidines, respectively

Fig. 4



Cl
O
NO2
NH2
Et3N, CH2Cl2
HN
O
NO2
H2N
N
H
NH2
99
HN
H
N
NH2
9

Fig. 5



O
S
Cl
O
+
H2N
H
N
NH2
99
Et3N, CH2Cl2
O
S
O
H
N
NH2
15

Fig. 6

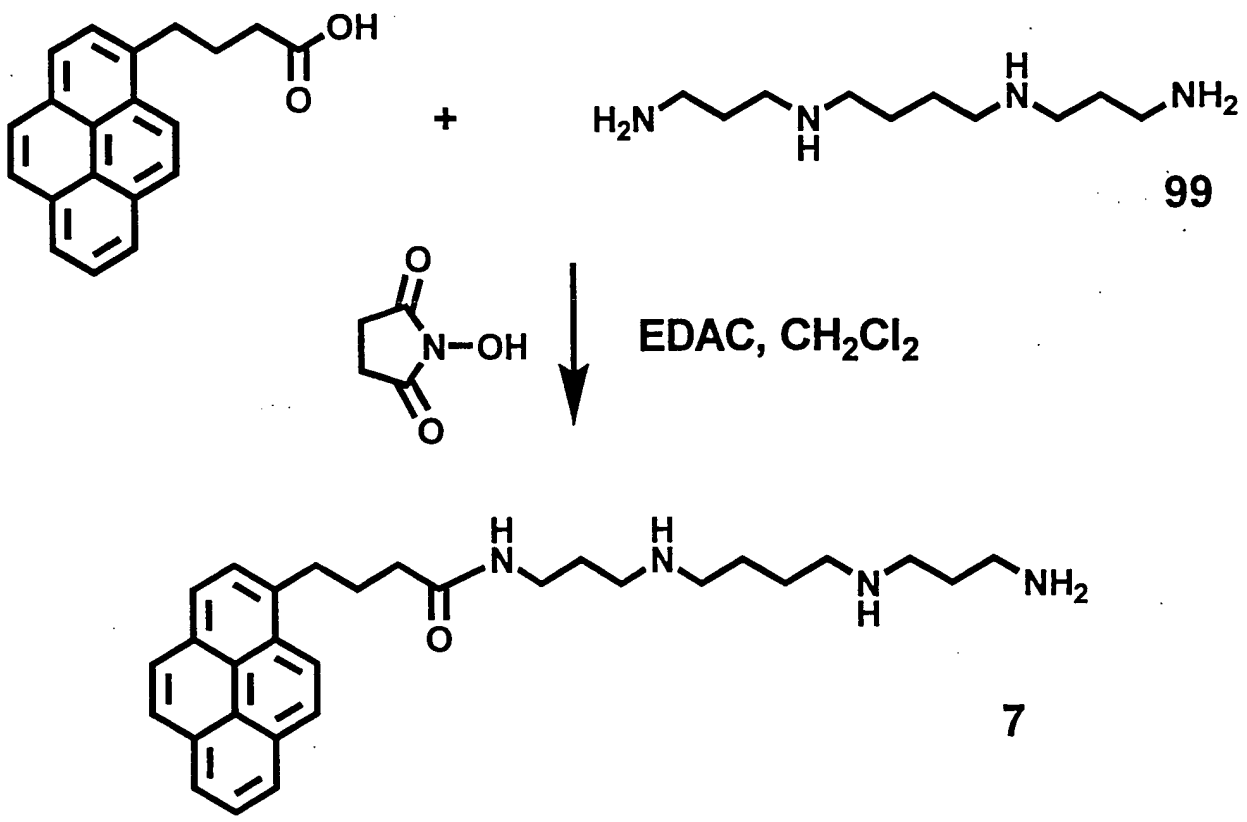


Fig. 7

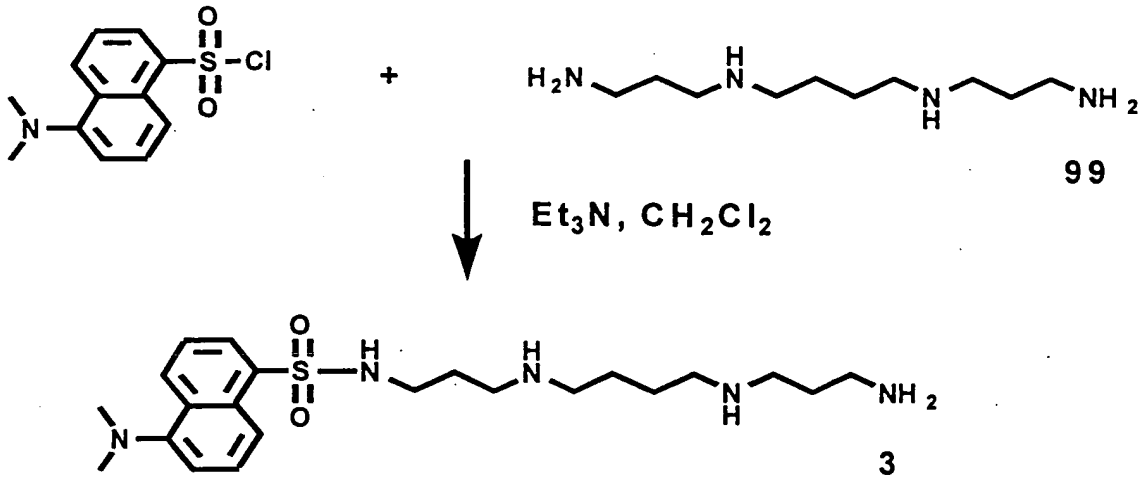


Fig. 8

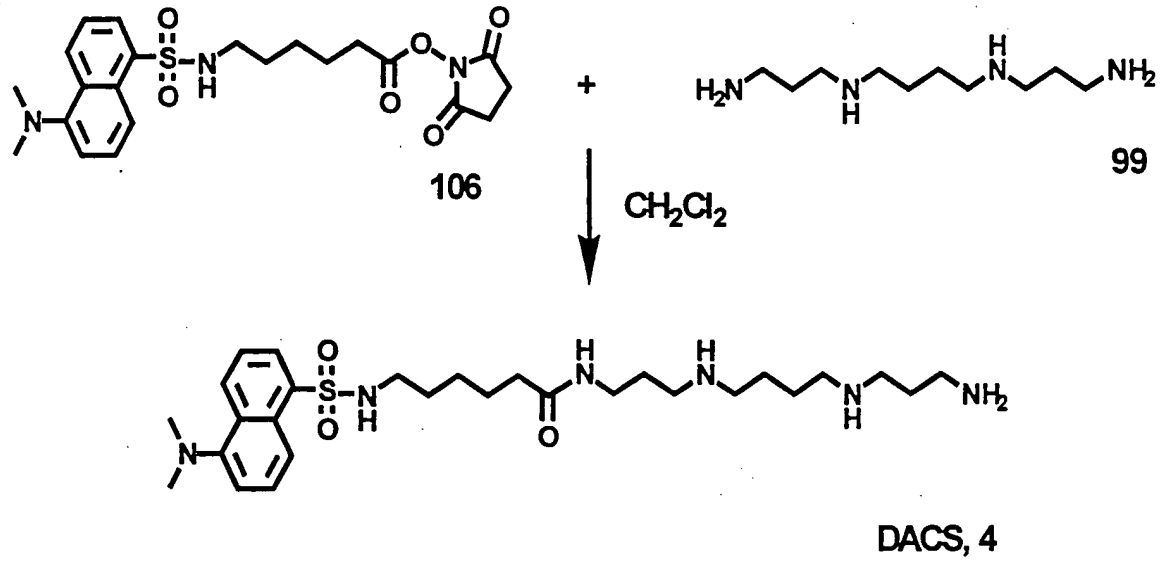


Fig. 9

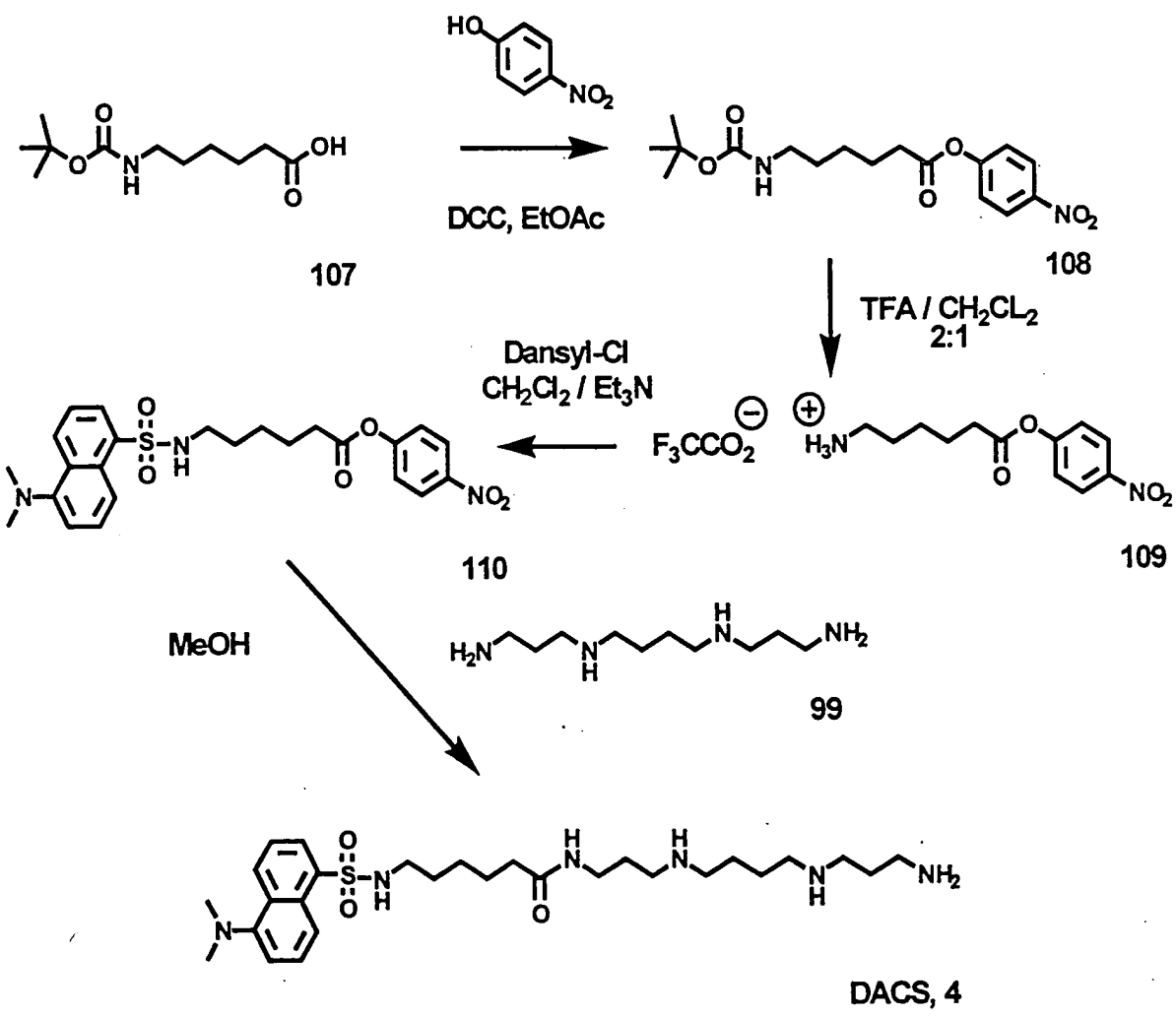


Fig. 10

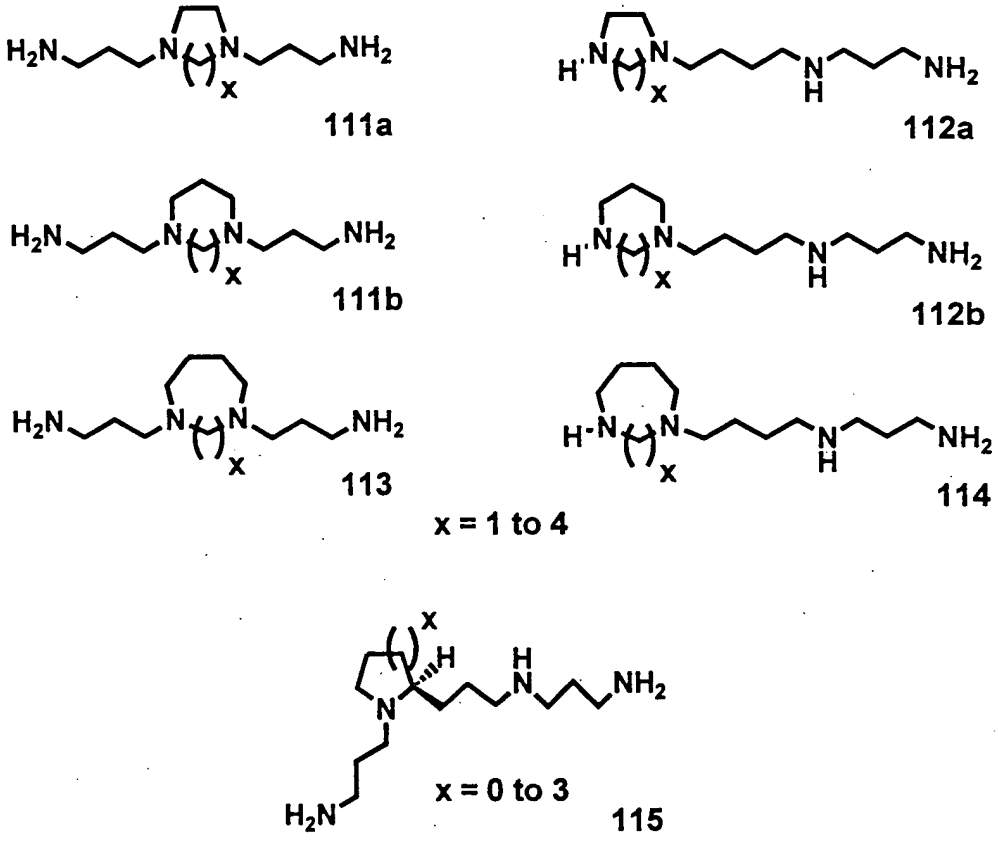


Fig. 11

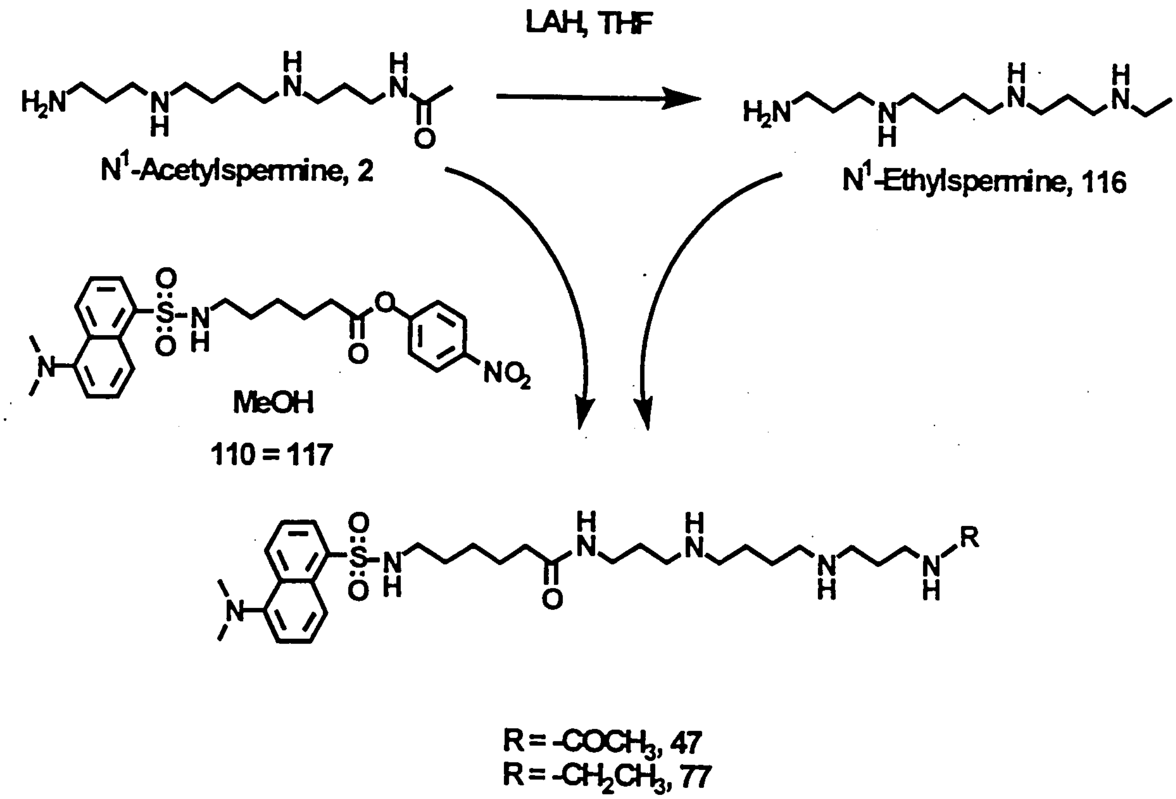

LAH, THF
N1-Acetylspermine, 2
N1-Ethylspermine, 116
MeOH
110 = 117
R = -COCH3, 47
R = -CH2CH3, 77

Fig. 12

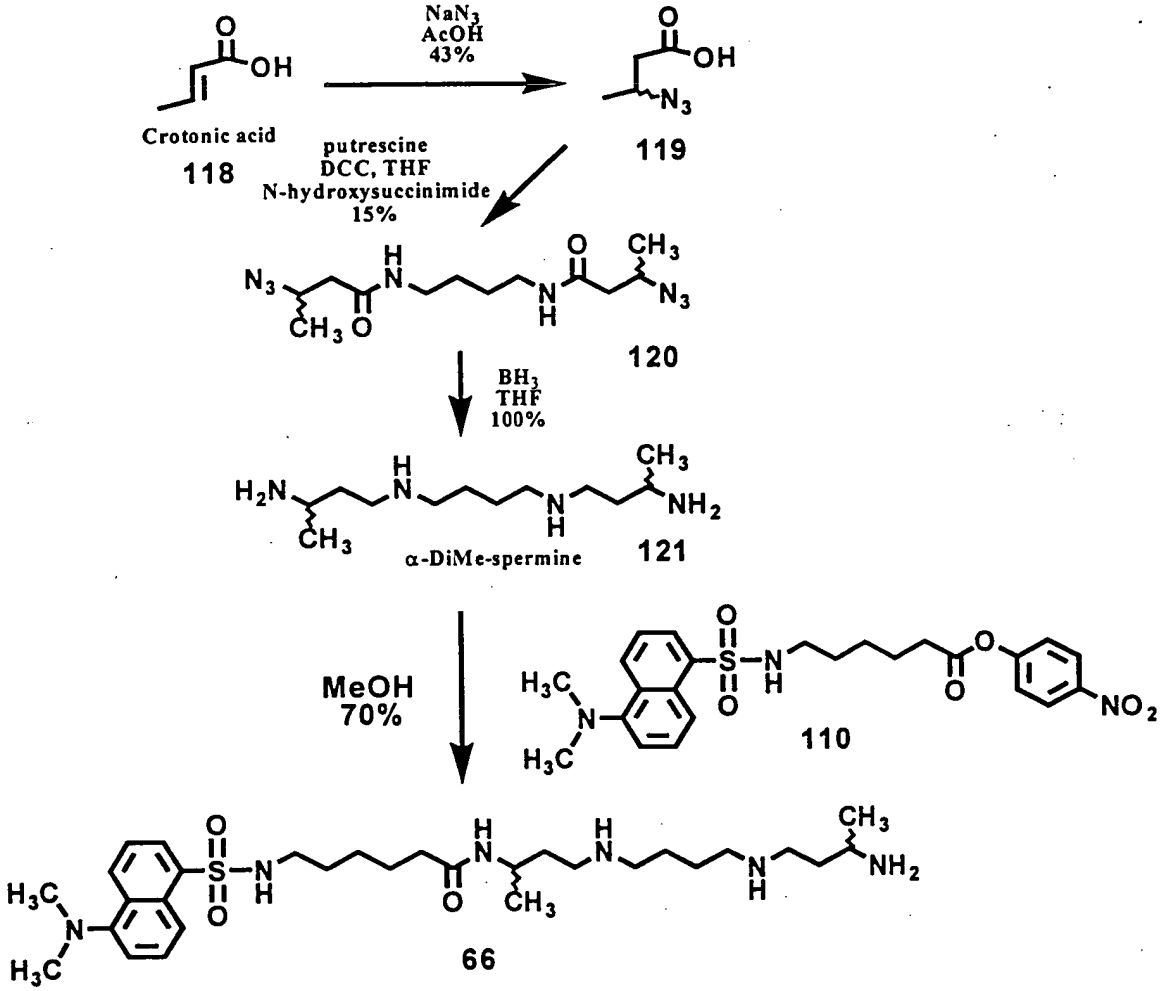


Fig. 13

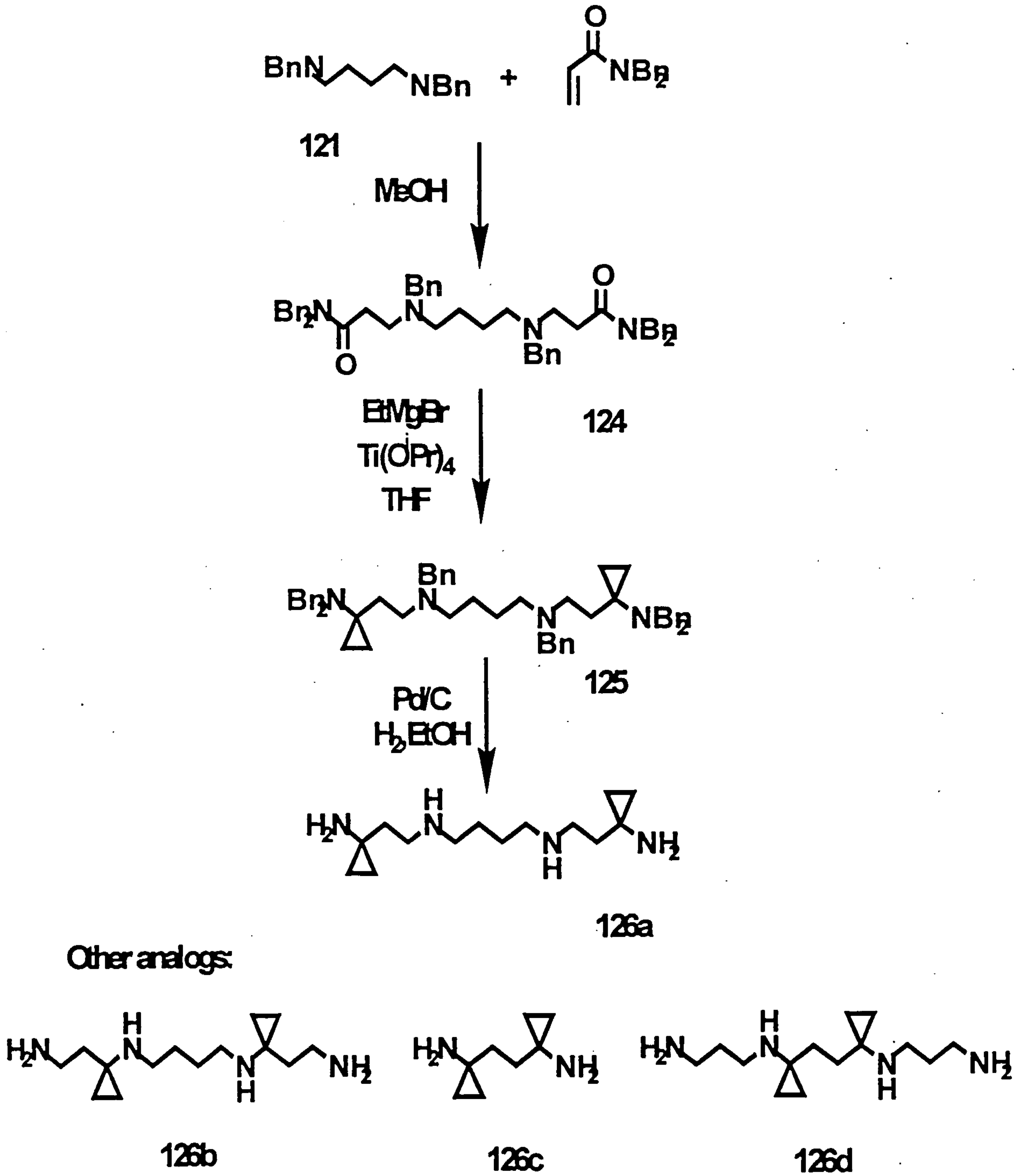
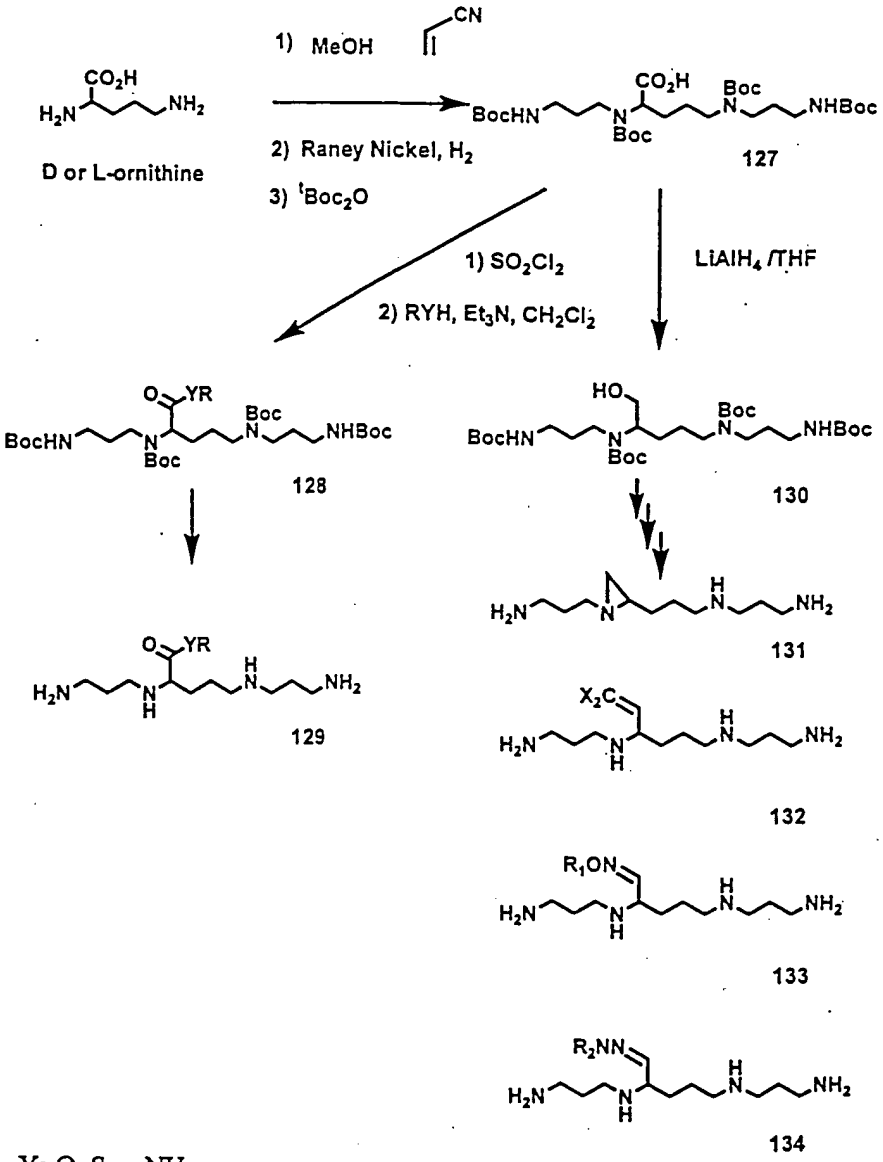

BnN
NBn
NBn2
121
MeOH
Bn
Bn2N
NBn2
124
EtMgBr
Ti(O^iPr)4
THF
125
Pd/C
H2, EtOH
H2N
NH2
126a
Other analogs:
126b
126c
126d

Fig. 14



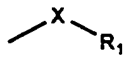
where Y=O, S or NH;

R= various groups including: propylaziridine, propylamine, hexyldansylsulfonamide

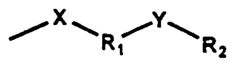
R_1=H, $CH_3(CH_2)_n$-, where n=1 to 10;

X =H or halogen

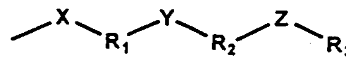
Fig. 15



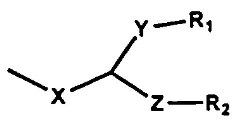
135



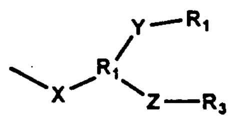
136



137



138

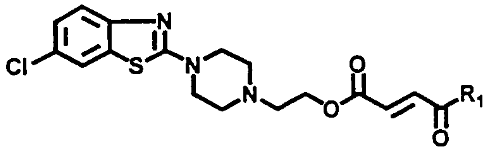


139

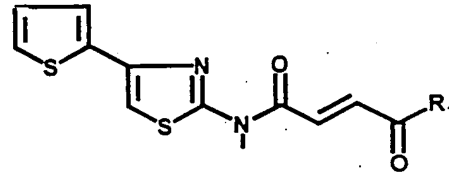
Where X=spacer$_1$; Y=spacer$_2$; and Z=spacer$_3$; and

R_1, R_2, and R_3 can be alicyclic, aromatic, or heterocylic

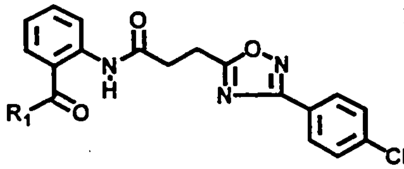
Fig. 16



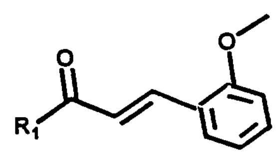
140



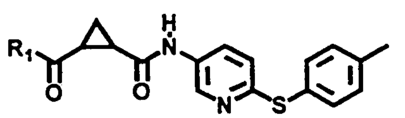
141



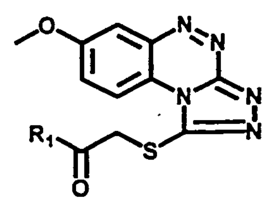
142



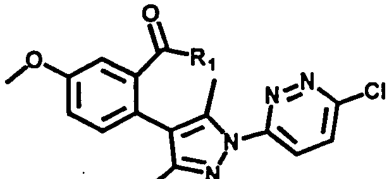
143



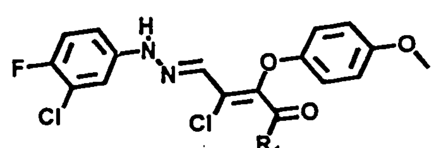
144



145



146



147

Fig. 17

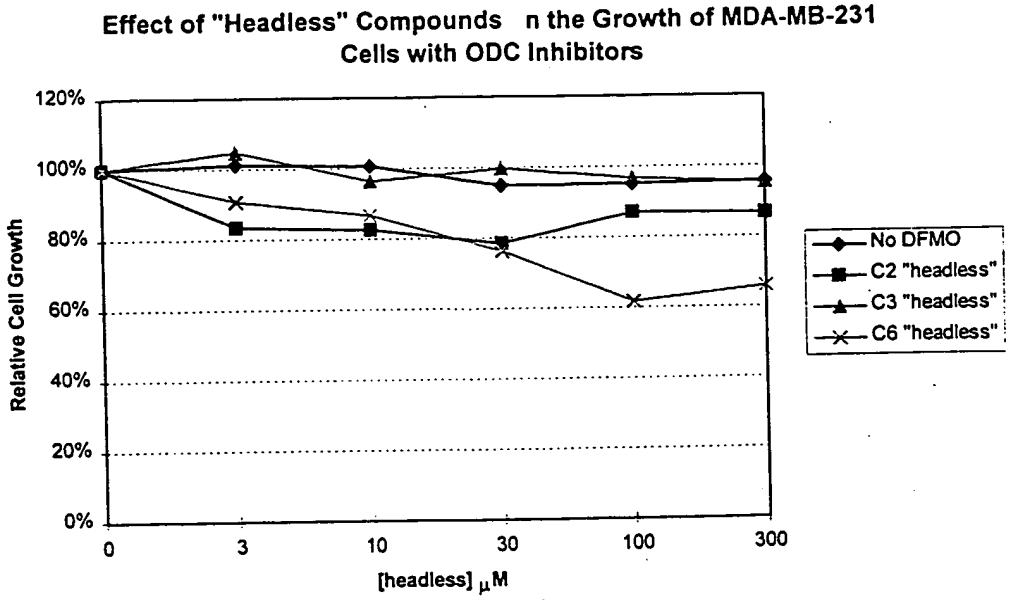


Fig. 18

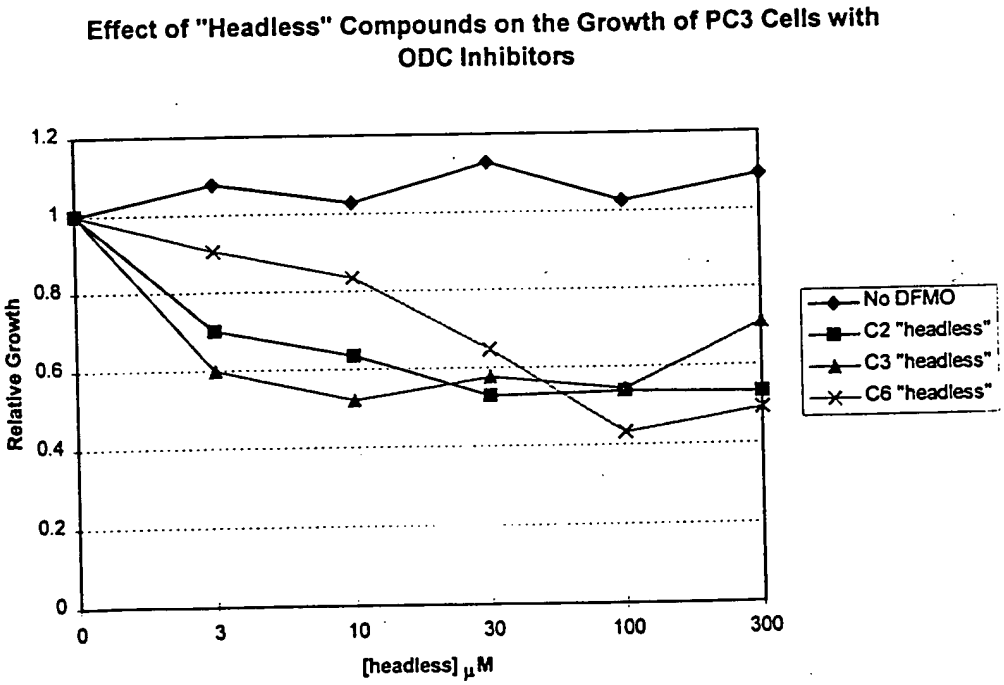
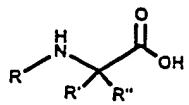
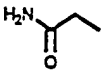
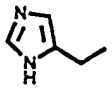
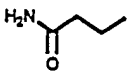
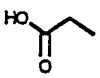
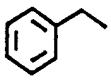
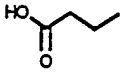
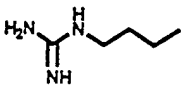
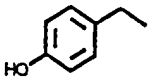
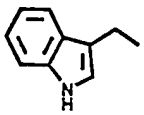


Fig. 19



153

stereochemistry:
L is S, D is R

R'		R'		R'	
-H	Gly		Cys		Ser
$-CH_3$	Ala		Met		Thr
	Val		Asn		His
	Leu		Gln		Pro
	Ile		Asp		Lys
	Phe		Glu		Arg
	Tyr		Trp		

Where R=head group; R"= H, $-CH_3-$, $-CH_2CH_3$, $-CHF_2$

Fig. 20

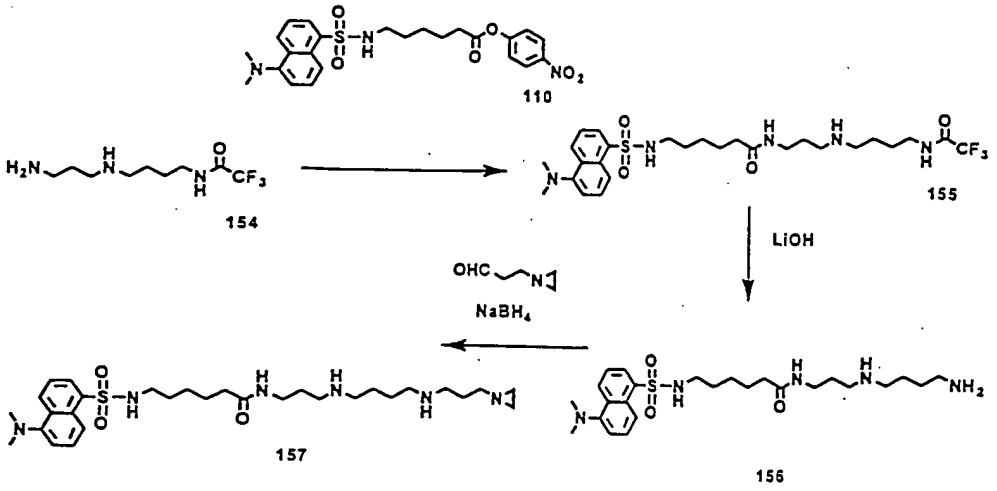


Fig. 21

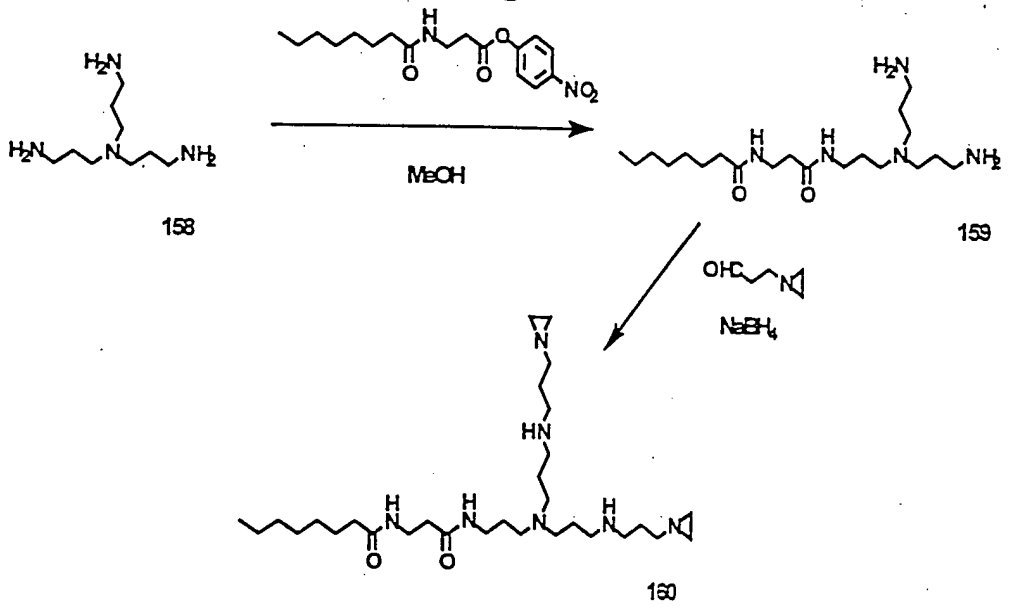


Fig. 22

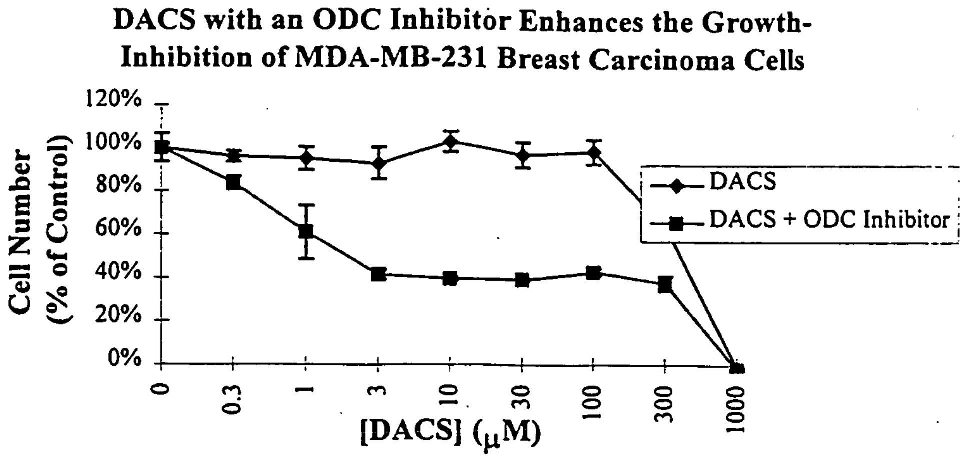


Fig.23

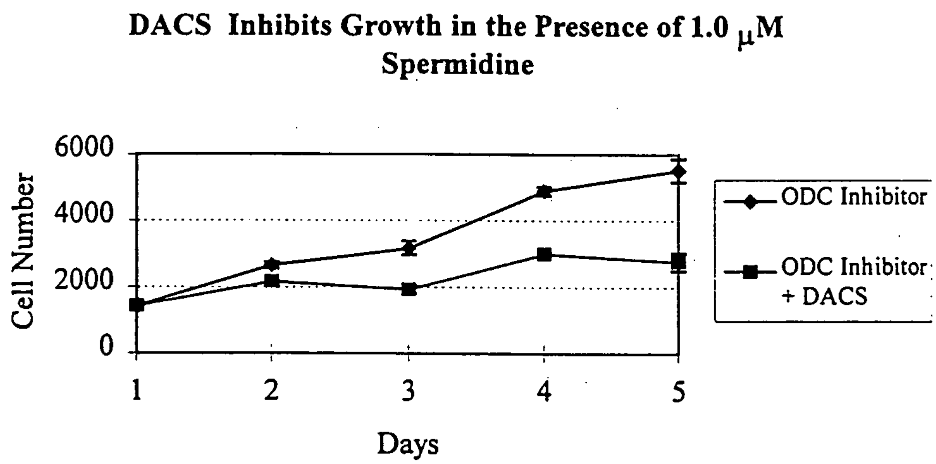


Fig. 24

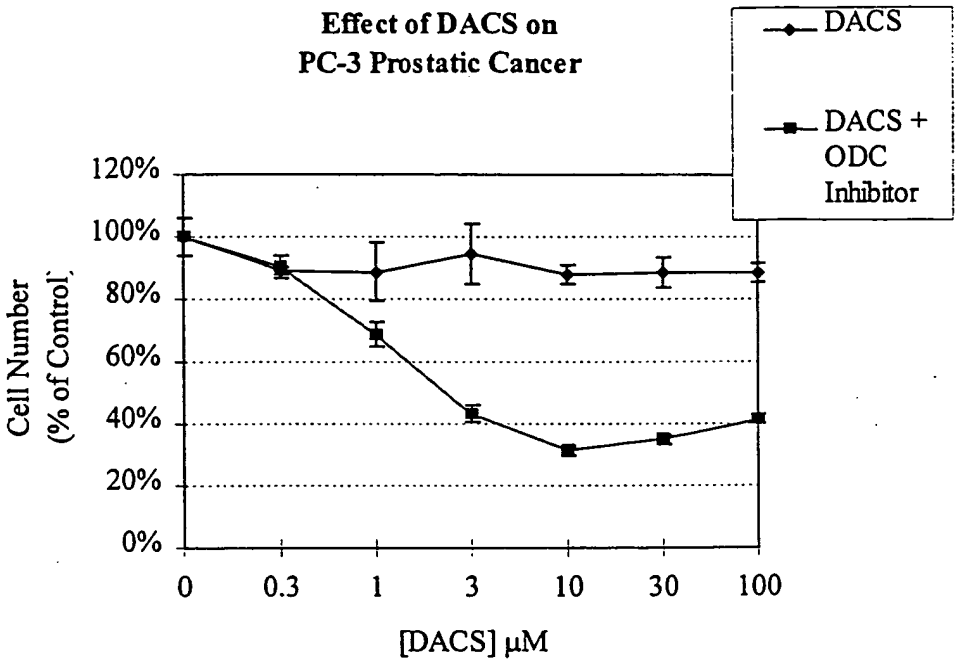
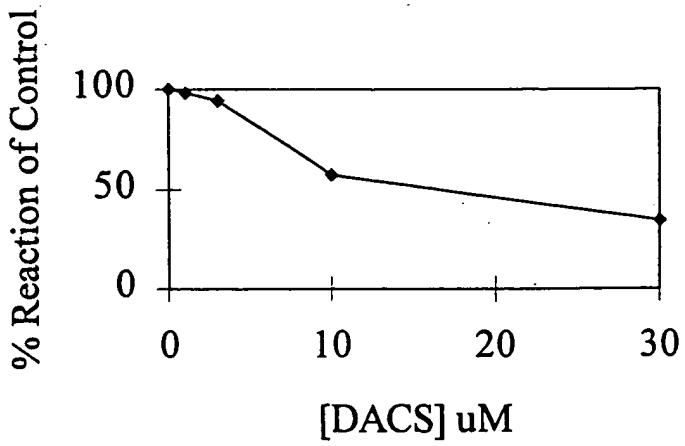
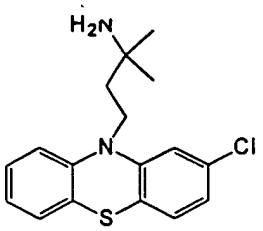
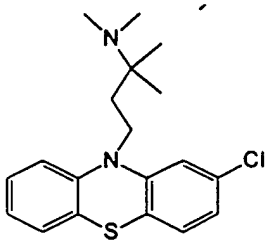

Effect of DACS on
PC-3 Prostatic Cancer
DACS
DACS + ODC Inhibitor
120%
100%
80%
60%
40%
20%
0%
Cell Number (% of Control)
0
0.3
1
3
10
30
100
[DACS] µM

Fig. 26

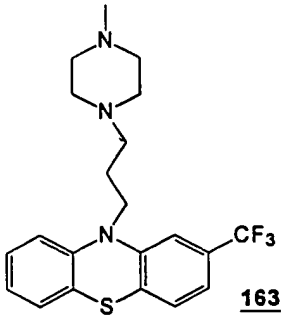

100
50
0
% Reaction of Control
0
10
20
30
[DACS] uM



161



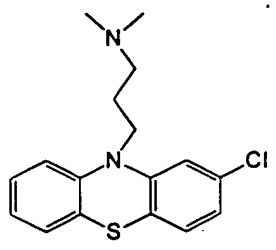
162



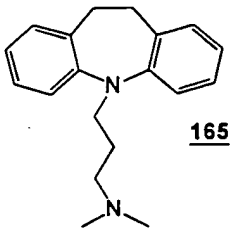
163

trifluoperazine

164

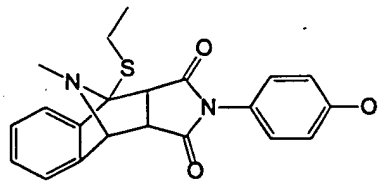


Thorazine



165

Imipramine



166

Fig. 25

Fig. 27

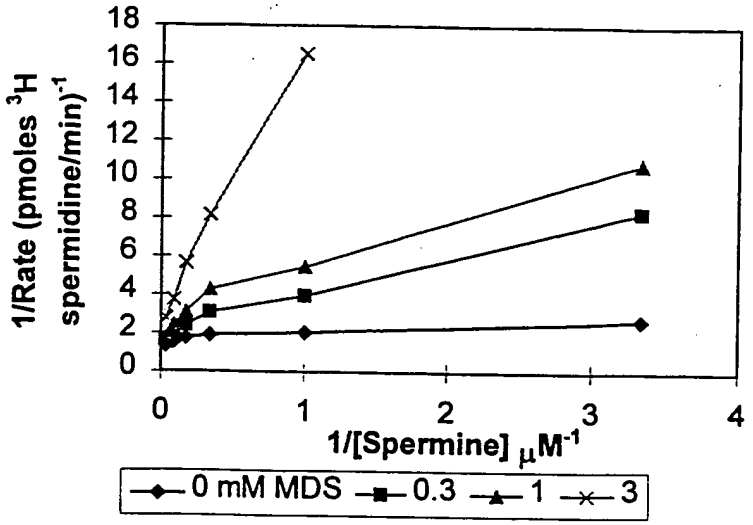

1/Rate (pmoles ^{3}H spermidine/min)$^{-1}$
18
16
14
12
10
8
6
4
2
0
0
1
2
3
4
1/[Spermine] μM^{-1}
0 mM MDS
0.3
1
3

Fig. 28

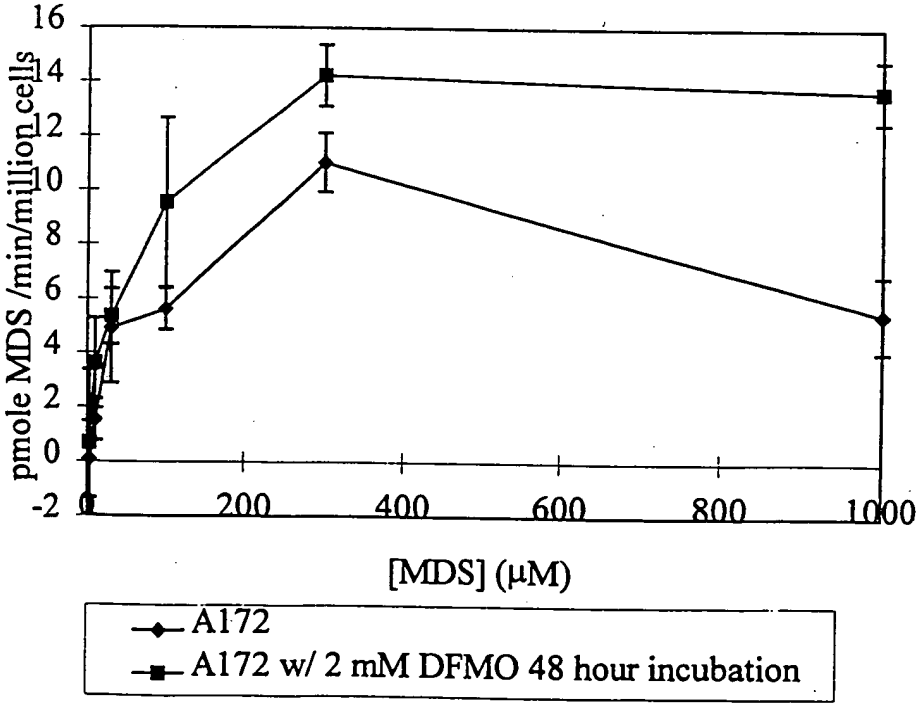

pmole MDS /min/million cells
16
14
12
10
8
6
4
2
0
-2
200
400
600
800
1000
[MDS] (μM)
A172
A172 w/ 2 mM DFMO 48 hour incubation

Fig. 29

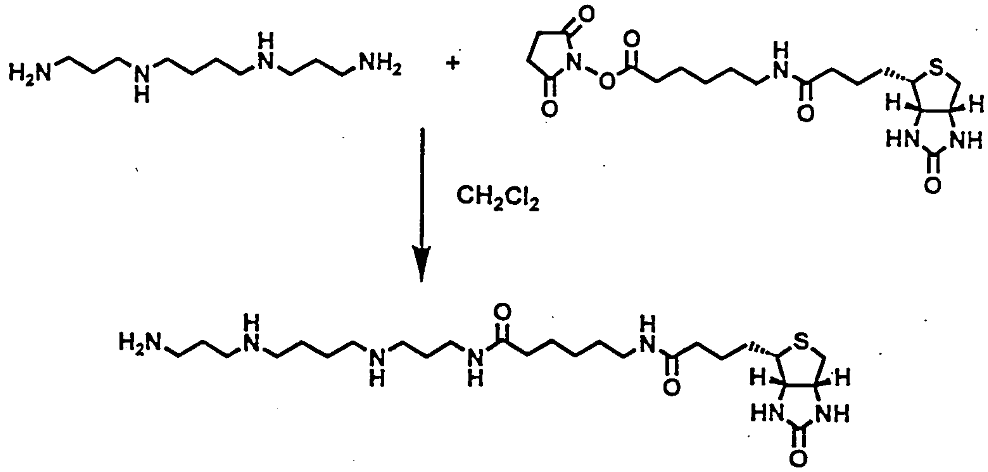


Fig. 30

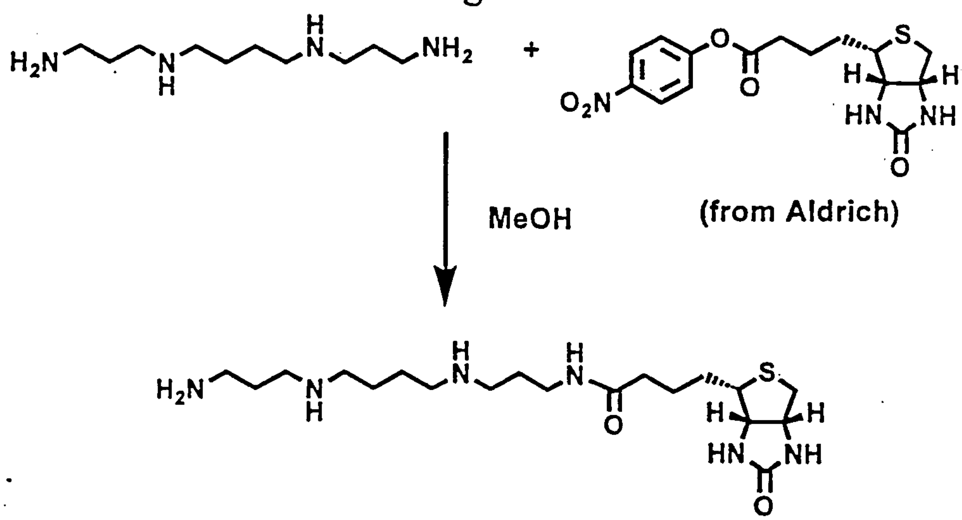
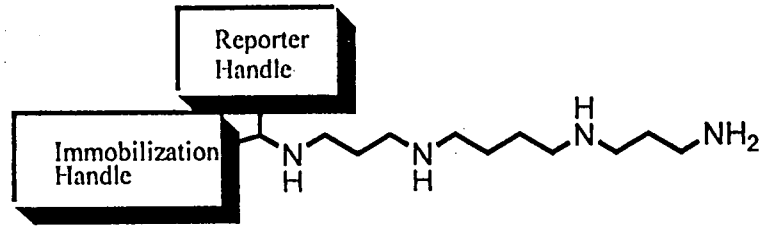
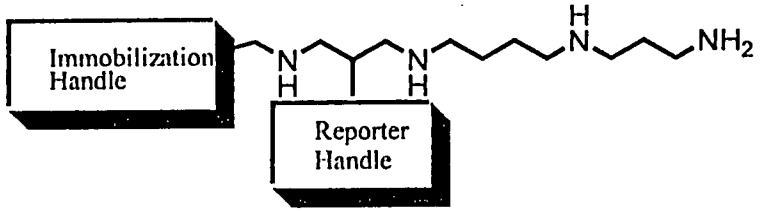


Fig. 31

A. Reporter and Immobilization handles are both N^1-terminal



B. Reporter Handle is internal and Immobilization handle is N-terminal.



C. Immobilization and Reporter handles are both N^1 and N^{12} terminal, respectively

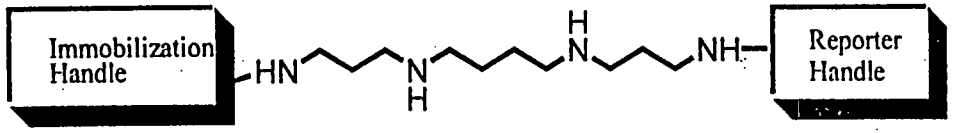


Fig. 32

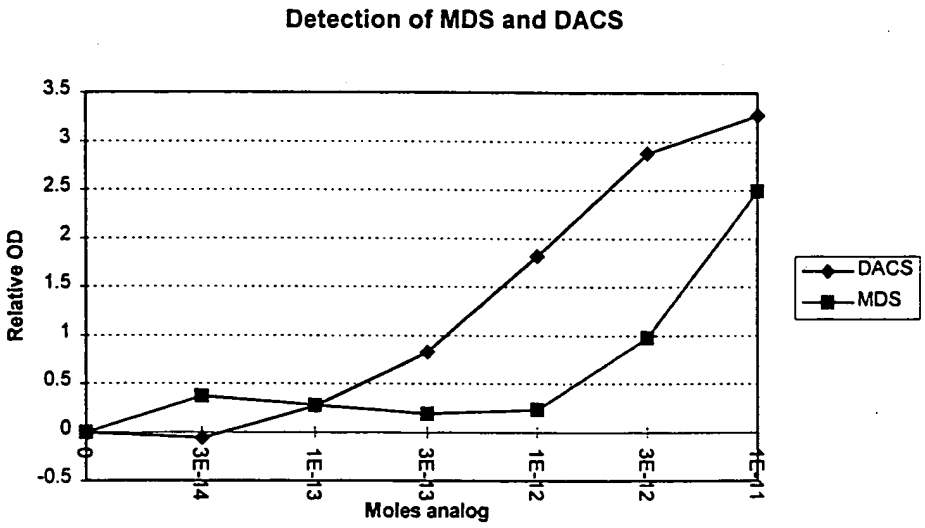
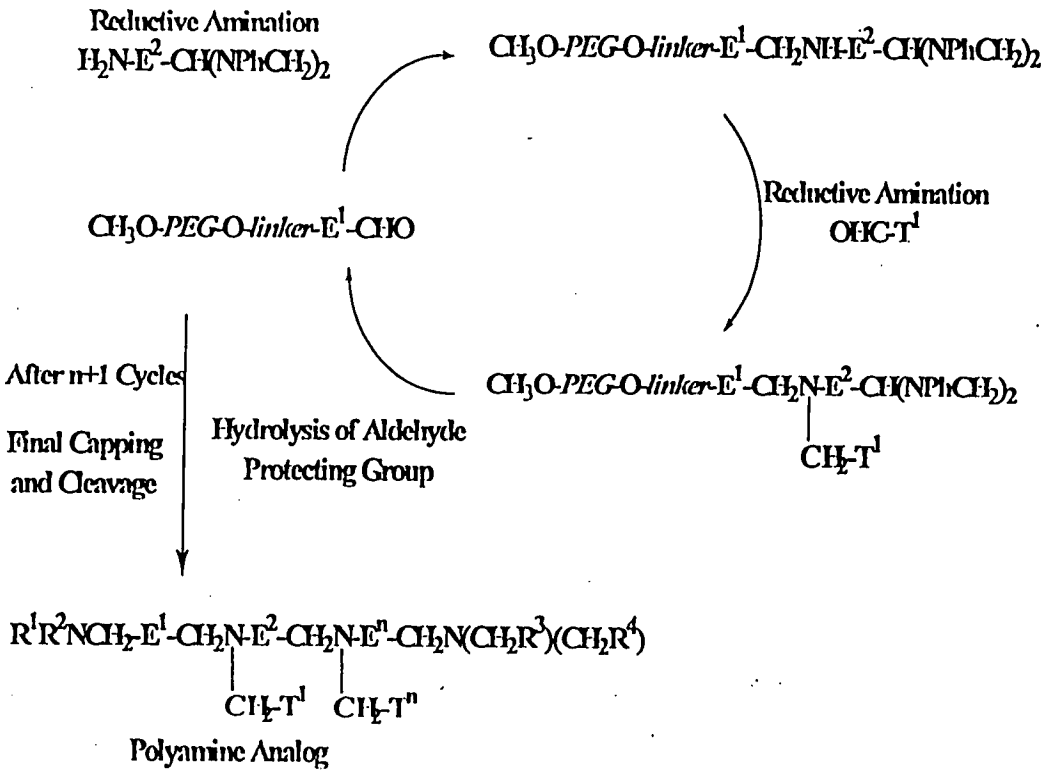


Fig. 33

General Scheme



E = Extender
T = Terminator

Fig. 34

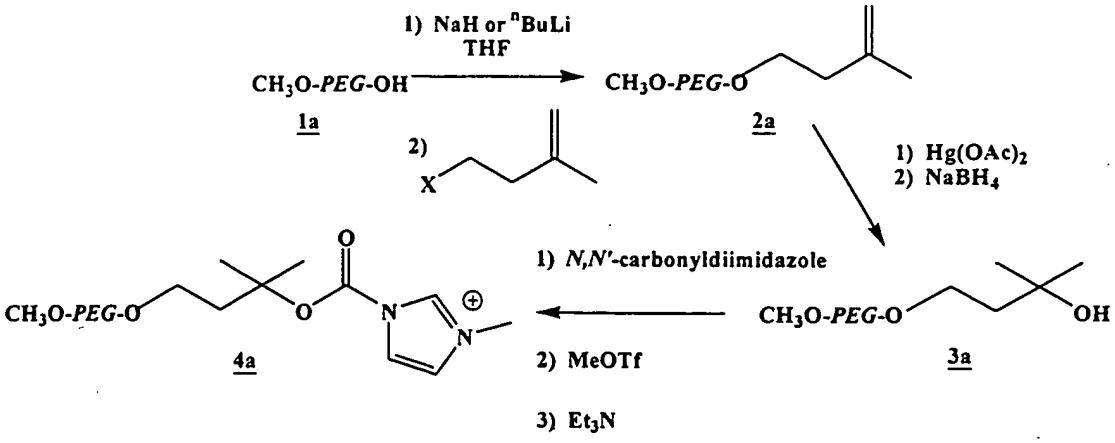

1) NaH or nBuLi
THF
CH3O-PEG-OH
1a
CH3O-PEG-O
2a
2)
X
1) Hg(OAc)2
2) NaBH4
1) N,N'-carbonyldiimidazole
CH3O-PEG-O
OH
3a
2) MeOTf
3) Et3N
CH3O-PEG-O
4a

Fig. 35

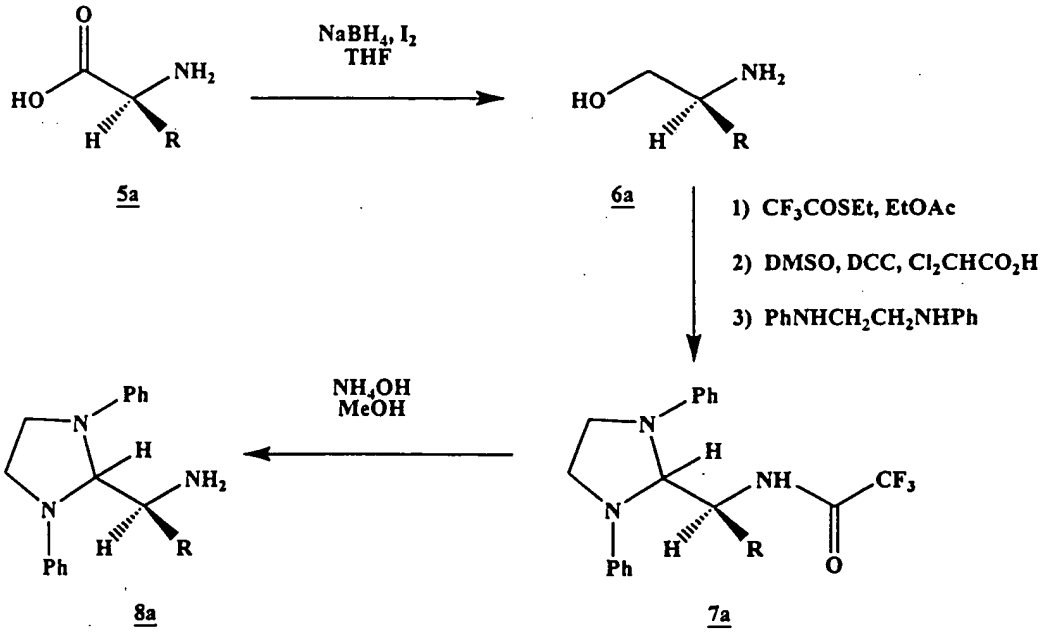

NaBH4, I2
THF
HO
NH2
H
R
5a
6a
1) CF3COSEt, EtOAc
2) DMSO, DCC, Cl2CHCO2H
3) PhNHCH2CH2NHPh
NH4OH
MeOH
Ph
N
H
NH
CF3
O
8a
7a

Fig. 36

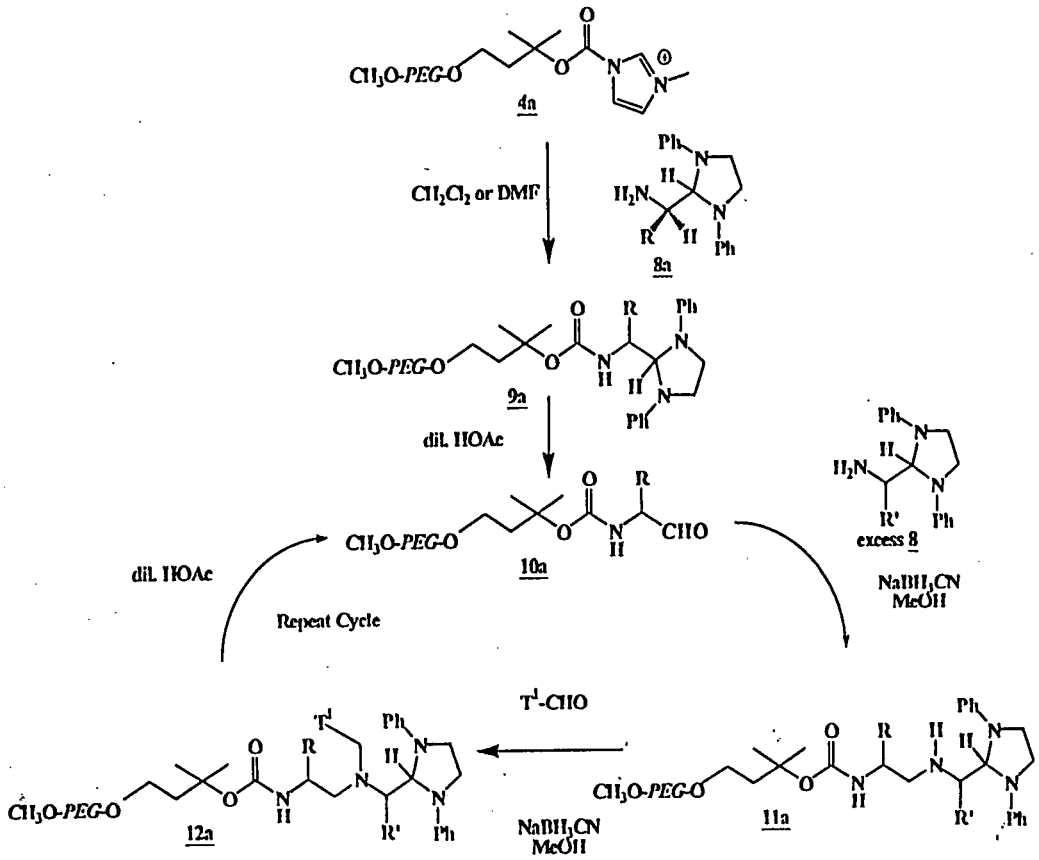


Fig. 37

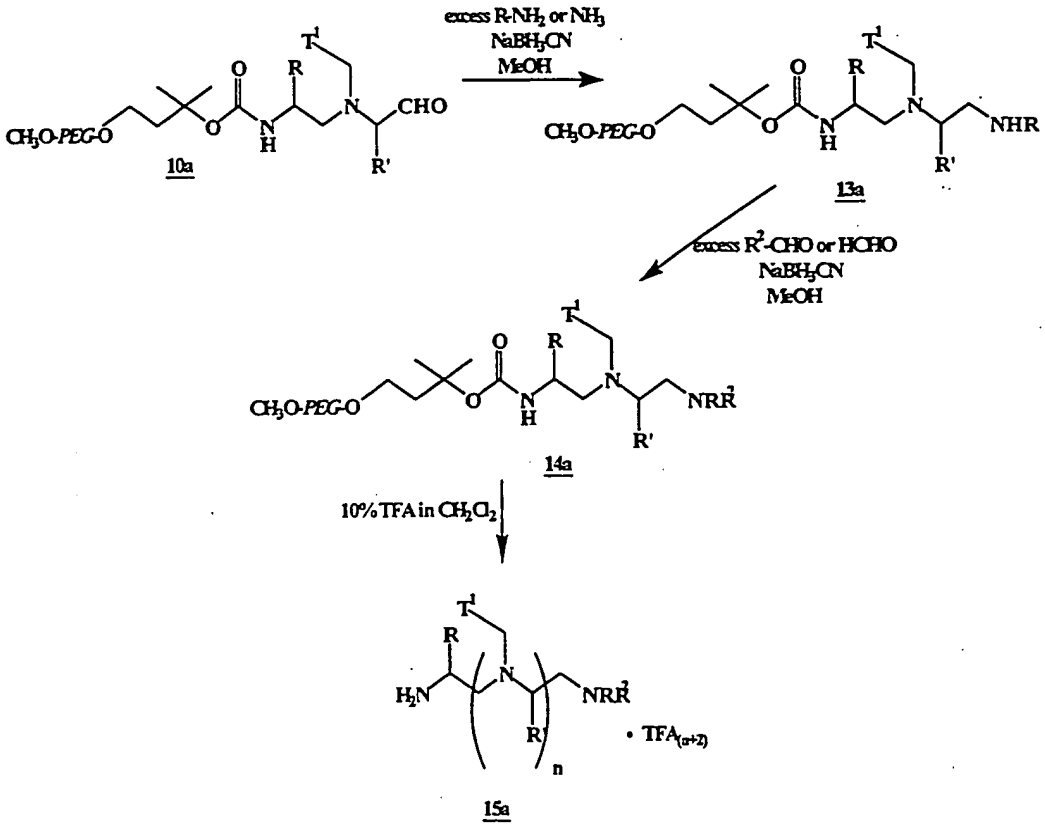
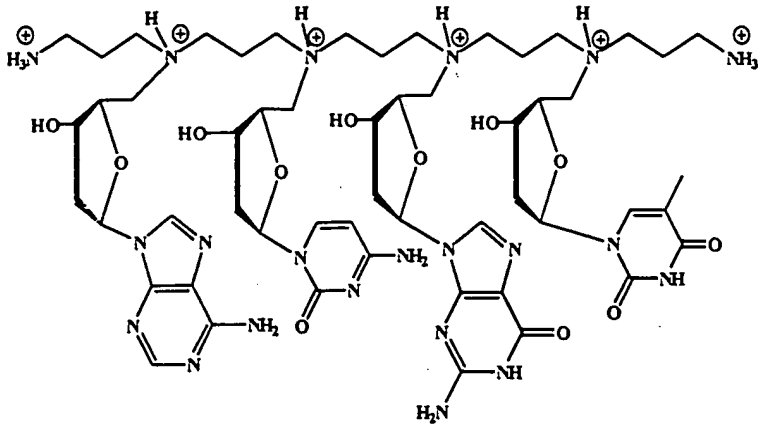

excess R-NH2 or NH3
NaBH3CN
MeOH
CH3O-PEG-O
10a
13a
excess R2-CHO or HCHO
NaBH3CN
MeOH
14a
10% TFA in CH2Cl2
15a
• TFA(n+2)

Fig. 38



Other Base / Polyamine Linkers As Terminators

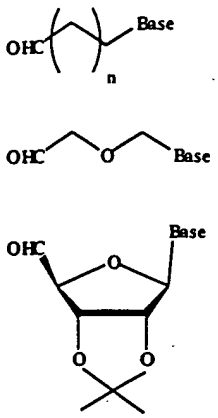


Fig. 39

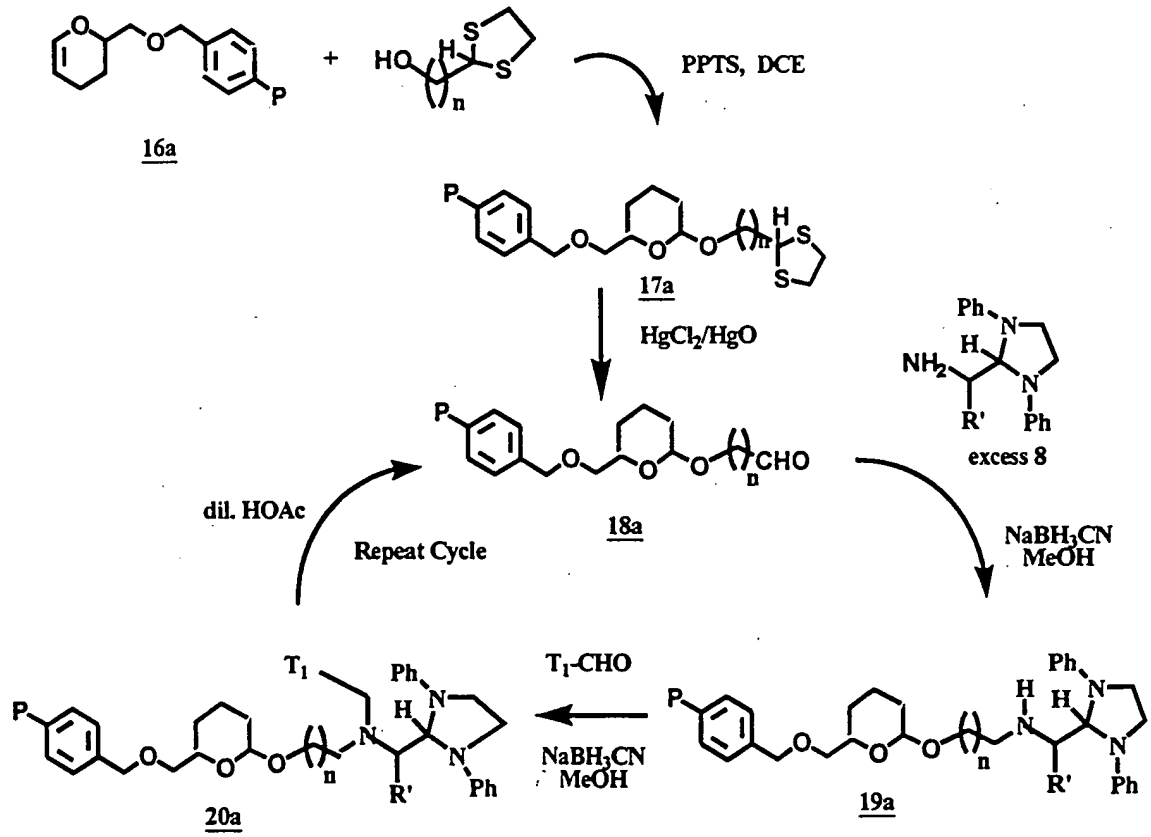
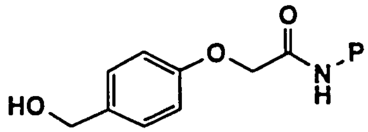


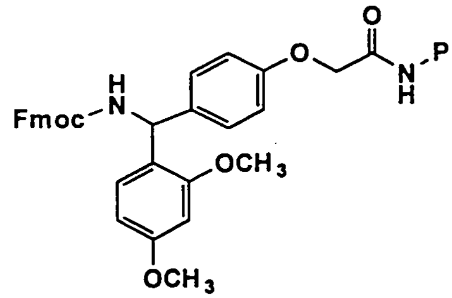
Fig. 40

Fmoc-NH-P

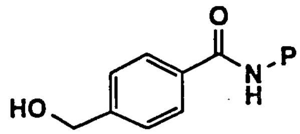
21a



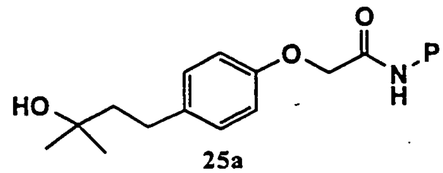
22a



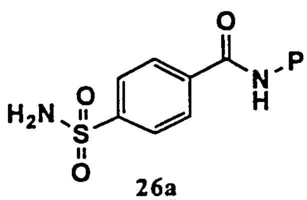
23a



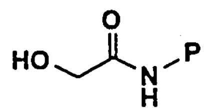
24a



25a

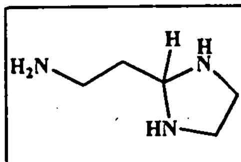
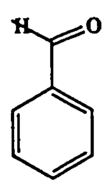
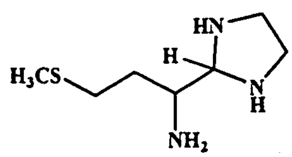
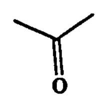


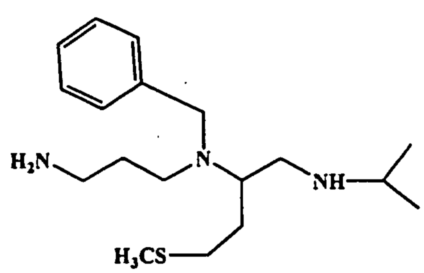
26a



27a

Fig. 41

 27a	 28a	 29a	 30a



31a